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A study of cochlear potentials

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A STUDY OF COCHLEAR POTENTIALS

by

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TABLE OF CONTENTS

TABLE OF CONTENTS - Continued

LIST OF FIGURES

LIST OF TABLES

CHAPTER I

REVIEW OF PREVIOUS INVESTIGATIONS

At least 400 papers and books have been written, entirely or in part, on the electrophysiology of the cochlea and the auditory nerve. The original or abstracts of 374 of them have been reviewed in preparation for this chapter. Of these, 271 are concerned primarily with electrical responses of the cochlea and nerve, 72 treat electrical responses as a side item, and 31 deal with hearing by electrical stimulation. In addition, 27 papers were examined which discuss electrical responses to sound from non-cochlear structures: from vestibular organs, tactile organs, and from animals without true cochlea or lagena.

To review each article critically is obviously impractical. Instead, the results of the investigations will be listed with special attention given to those results which relate to the experiments and conclusions reported in this dissertation. Critical comments will be added when necessary. Also to be discussed are the conclusions from the literature about the origin of the electrical responses and their significance, and about stimulation of the auditory nerve.

A. Periods of Investigation

Beauregard and Dupuy (32) reported the first recording of electrical responses from the auditory nerve (N VIII). They placed one electrode on the cut section of

the nerve of a guinea pig or frog and the other on the tympanic membrane. A galvanometer completed the circuit. Whistles furnished the sound stimulus. Responses, indicated by reduction and reversal of the demarcation current, were small but definite. Beauregard and Dupuy found high tones more effective than low tones but they did not calibrate either their accustic or their recording system.

Succeeding experiments in this early period, using sound as the stimulus and a galvanometer as the recording instrument, were done by Piper (314, 315, 316) who detected electrical responses from the saccular otolith of fish; by Buitendijk (61) who picked up responses from the auditory nerve (N VIII) of rabbits and guinea pigs; by Forbes, Miller and O'Connor (154), recording electrical responses from the medulla of a cat; and by Foà and Peroni (153) who detected electrical responses at an electrode on the facial nerve trunk of a turtle.

The second period had a clear-cut beginning with the work of Wever and Bray (394). They used more powerful amplification than had been employed previously and they used a telephone receiver as the detector. They placed one electrode on N VIII of a cat and the other on indifferent tissue. What came back through the telephone receiver was a sound closely resembling the stimulus to the cat's ear; pure-tone frequencies were reproduced exactly and speech was intelligible. Wever and Bray established that these were physiological responses and not artifacts. They attributed

this phenomenon to the action currents of N VIII.

Adrian (1) suggested a "microphonic" action of the inner ear as the explanation of the "Wever and Bray effect" but he soon reversed his interpretation (10) and supported Wever and Bray's original contention. Davis and Saul (119) confirmed that this microphonic behavior recorded from N VIII is diffuse electrical spread from the cochlea. They pointed out (120, 121, 348) that the Wever and Bray effect is a composite of action currents from the nerve and microphonic "spread" from the cochlea. Period II was terminated by Davis's restatement (98) of this dual concept and by his description of the characteristics of both components. There were some disagreements after 1934 but they rapidly lessened and there have been no serious challenges to the interpretation.

Period III had no clear beginning; it fused with the latter part of the second period. In this period (1934-1950) experiments involving the electrophysiology of the cochlea and auditory nerve dealt with (1) the nature of the electrical responses, (2) the study of auditory bio-physics, physiology of hearing, and auditory theory, and (3) the pathology of hearing. The results of this period will be covered in detail in the discussion of the electrical responses.

Period IV also has no clear beginning. It merges with the latter part of period III, which cannot be considered fully concluded. It can be characterized, however, by new

approaches or new phenomena in Békésy's investigations of the electrical properties of the ear and the nature of the electrical responses from it (36, 37, 38, 39), in Davis and co-workers' identification and description of the summating potential (113, 188), and in Galambos, Rosenblith and Rosenzweig's argument for a cochleo-cochlear pathway (169).

Investigators did not confine their experiments to the common laboratory animals, cats and guinea pigs. They experimented on humans, monkeys, dogs, rabbits, opossums, bats, rats, and hamsters; the reptiles: turtles, frogs, alligators, and lizards; pigeons and grouse among the birds; and on several species of fish. Even the grasshopper family and cockroaches were tested. These insects have no true cochlea or lagena but do have receptors which seem to act as sound detectors.

In mammals and birds recording electrodes have been placed chiefly on the round window but many other parts of the auditory apparatus have been explored: the oval window and footplate of the columella; all regions of the bony capsule and, in more recent years, within the bony capsule; the promontory, semicircular canals, external auditory meatus, internal auditory meatus; the auditory nerve and surrounding tissues; and many places within the brain stem.

B. Terminology

Electrical activity from the neural structures has been called "action potential" or "action current" depending

on which was being measured. The local cochlear action has been called many things. Adrian popularized two terms: the "Wever and Bray effect" (10) and "microphonic" (1). Other names given were; "bio-microphonic" (265), "spread" from the cochlea (120), "cochlear effect" (155), "cochlear potentials" (261), "cochlear response" (42), "aural microphonic" (361) and "cochlear microphonic" (331).

In this report "action potential" (AP) will be used because in the experiments at the Central Institute for the Deaf potential changes of the nerve are measured. Most investigators have measured potential changes. Action currents can be translated into potentials if resistance factors are properly accounted for. The local cochlear action will be referred to as "cochlear microphonic" (CM) because the action is so much like a microphone and because the effect is cochlear. These, too are potential measurements.

C. Nature of Responses - Normal

1. Localization of Responses.

Davis and Saul (122) localized action potential (AP) production to the auditory tracts. However, AP has been picked up at the round window and other places in the cochlea (115, 116, 288, 361). Lurie, Davis and Derbyshire (299) picked up responses in the cochlear nucleus from contralateral as well as from homolateral stimulation.

Cochlear microphonics (CM) have been picked up from many places in the vicinity of the cochlea as well as on and in it. Distance from the cochlea and conditions of

electrical conductivity determine the strength of CM which is recorded (108, 122, 206). Davis, Derbyshire and Lurie (106) note that the round window response referred to the neck is more intense than the response from any other non-penetrating position. Rosenblith and Rosenzweig (339) found certain "neutral" areas outside the cat's bulla where CM is not detectable, neutral in that displacement of the electrode to one side or the other brings back CM. The reference electrode was in the mouth of the cat.

Many investigators argue that each pure tone stimulates a restricted portion of the cochlea, at least at moderate intensities of stimulation. To study this question has been the reason for many of the experiments on the electrical responses of the cochlea. The positive conclusion that CM for each frequency has its lowest threshold in definite, restricted cochlear regions was reached in at least four sets of experiments on normal cochleas (91, 93, 259, 443). Using the technique of operative trauma to the cochlea, even more experimenters reached the same conclusion (92, 97, 111, 116, 362, 380, 381, 382). A less specific conclusion is that there is localization only in a general way for high tones in the basal portion of the cochlea, for low tones in the apical region, and for the intermediate tones in the intermediate portions of the cochlea; no localization for the very low tones, about 200 cps and below (30, 108, 118, 142, 206, 209, 299, 301, 360, 361, 379, 436). Work by McCrady, Wever and Bray (301, 302)

on the pouch-young opossum indicates that early inception of hearing for certain frequencies is correlated with a CM response to those frequencies and with early histogenesis of particular regions of the organ of Corti (OC). Galambos and Davis's work with single fibers of N VIII (164, 165, 168) shows that each fiber is particularly sensitive, especially at threshold, to a very narrow band of frequencies. Only Wever, Bray and Horton (415) and Gisselsson (184) report evidence for no localization.

2. Synchronization of A^P.

How well AP reproduces the frequency of a stimulating tone is determined principally by the refractory period of the fibers of the auditory nerve. Davis and Saul (120) and Davis, Derbyshire and Lurie (106), basing their estimation on the total activity of the nerve, figure the shortest possible refractory period to be no less than 1 msec. Stevens and Davis (361) say that the refractory period is not always constant but can lengthen with continued stimulation. Galambos and Davis (165) report a refractory period of 2 msec or more in single fibers but they were dealing with second-order neurons (168). The maximum rate of discharge was 450/sec with the usual adapted maximum at about 200/sec.

3. Frequency Reproduction by CM.

CM shows no sign of a refractory period (106). The highest frequency recorded was 98,000 cps, in the bat

(160, 162). This was the limit of the generator of the ultrasonics. The lowest frequency that Galambos recorded in the bat was 30 cps. Wever, Bray and Willey (426) report the lowest frequency recorded from any animal, 5 cps from the guinea pig. These lower limits were also set by limitations of the acoustic apparatus. Wiggers (440) reports even slower potential changes during contractions of the intraural muscles. Galambos (160) recorded the highest responses from a guinea pig, 40,000 cps. Extreme ranges reported for some other animals are: pigeon, 100 to 11,000 cps (404, 405); cat 35 to 25,000 cps (408); an upper limit of 3600 cps from the turtle (398) and of 600 cps from the frog (405).

4. Shape of Electrical Responses (AP).

The first description of the shape or pattern of AP was given by Buitendijk (61) as "two - or more phasical character." With both electrodes on N VIII Wever and Bray (396) found more distortion than when one electrode was on indifferent tissue, probably because of "diphasic" action currents from N VIII. Davis (98) says that AP is a diphasic wave with a monophasic character predominating. Wever (392) gives a more exact temporal illustration of AP response to a 300 cps pure tone. It is triphasic but an early negative spike dominates the picture. This is the temporal course he depicts (from his Figure 26): a negative maximum is reached at 0.45 msec after its start; there is a return to

the baseline at 0.75 msec, a small positive peak at 0.85 msec and a return to the baseline at 0.95 msec; there is a second negative peak at 1.08 msec and a gradual return to the baseline or zero potential which was not quite complete at 1.50 msec. Stevens and Davis (361) give the duration of AP as less than 1 msec. This corresponds closely to the diphasic portion of Wever's description. Davis et al (112, 116) say that the shape of AP at the round window (RW) is the same as that at other places in the cochlea.

5. Shape of Electrical Responses (CM).

That speech and tones are reproduced accurately by CM through a telephone or loudspeaker is stated without qualification by Bronzini (59), by Davis and Saul (110) and by Wever and Bray (386, 394, 395). Wever and Bray (396) found reproduction more distorted with both electrodes on N VIII and Davis et al (108) say that there is a metallic quality to speech because of the relative emphasis of frequencies between 800 and 2500 cps. Some authors report, with no qualifications, exact oscillographic reproduction of pure tones (14, 108, 160, 161).

Davis and Saul (122) claim accurate reproduction of wave form only above 800 cps. The complexity below that frequency they attributed, at first, to harmonics (110, 122). For very low frequencies (60 cps and below) there is much harmonic distortion (426) but most of the distortion in the

wave form below 800 cps has since been ascribed to the presence of AP (53, 98, 104, 299). Davis, Derbyshire and Lurie (106) conclude that the total electrical response from the round window (RW) is the algebraic sum of AP and CM, with AP making up 20-30% of the total (98, 128).

6. Polarity.

With an electrode on the round window (RW) or other part of the cochlea and a reference electrode on the muscles of the neck, AP is diphasic with an initial negative spike (116, 361). Davis and co-workers (98, 104, 109) report that the initial negative spike always maintains the same polarity regardless of the phase of the initial stimulating wave at the eardrum. AP following a brief click also is negative not only at the RW but at all portions of the cochlea that were investigated (116, 118).

Davis et al (109) discovered that CM could be either positive or negative. With positive pressure in the external auditory meatus the RW becomes negative with respect to the muscles of the neck and positive with a rarefaction in the meatus. These same relations hold true for scala tympani and are opposite for scala vestibuli, scala media, apex and oval window.

The polarity of scala tympani of the first turn (It) is practically the same as that of the RW (116, 118). Scala media and scala vestibuli show the same polarity as each other and in the first turn (Im and Iv) the responses

are almost the same as at the oval window. The oval window leads the RW in phase by 130° at 705 cps, 152° at 1200 cps, 150° at 2000 cps, and 193° at 3000 cps, according to Davis et al (109); the average is 156°. Stevens and Davis (360) later describe an opposite trend with a phase difference of 180° for low frequencies decreasing to about 90° at 4000 cps.

Davis, Gernandt and Riesco-MacClure (115) attribute a lack of exactly opposite phase relations on opposite sides of the basilar membrane to electrical leakage from other channels. Bleeker and de Vries (44) found no difference in phase between the responses from electrodes on the RW and on the footplate of the columella of the pigeon. However, when they removed the electrode from the footplate and placed it in one of the semicircular canals there was a difference in phase.

7. Relations to Intensity (AP).

Even though the distinction had been made between CM and AP it was still difficult to measure each component separately. Nevertheless, many measurements were made of the amplitude of responses with changes of the stimulus strength in decibels. The resulting curves for AP resemble the Weber-Fechner curves for the increase of sensation with intensity (98, 106, 107). Increase in magnitude of AP is rapid but AP reaches a definite limiting value (98, 107, 361). This maximum is reached at the same intensity necessary for CM to reach its maximum, according to Davis and co-workers (98, 109, 361). They say that CM also parallels AP

in its pattern of growth (106, 109, 128).

With newer techniques Davis, Gernandt and Riesco-MacClure (115) examined AP by itself. They report a rapid increase in amplitude with an increase of the stimulus beyond threshold. A two-fold increase in acoustic pressure more than doubles the amplitude of AP. A maximum of about 50 μV is reached within 30 db of its threshold. Hawkins (218) shows an inflection in his curve of the linear value of AP versus the logarithm of the stimulus. It comes at approximately 30 db above an extrapolated threshold for the click stimulus. The secondary rising portion may indicate the bringing in of a new set of neural elements (361, Figure 148 B). Davis et al (116) found nearly the same sized maximum for AP at all positions that they explored: RW, apex, and various turns and scalas in between.

Galambos and Davis (164, 165, 168) working with single cells of the cochlear nucleus, found that a change of intensity of a sound of constant frequency is reflected in the rate of discharge. The maximum unadapted rate of 450 spikes/sec is attained at about 30 db above the threshold for the neural element. Two hundred per second is a more usual maximum for most units. The rate of discharge plotted against the logarithm of the stimulus strength gives a sigmoid curve. This pattern, except for the maximum rate of discharge, is the same for the completely adapted units as well as for the unadapted or partially adapted ones.

report extremes of 1.6 and 0.54 in guinea pigs. However, the average in each of the papers reviewed is very close to 1.0. For pigeons, slopes have been reported from 0.53 to 0.35 (43, 390, 404). Bray and Thurlow (54) used a wave-analyzer as a voltmeter and measured responses from pigeons below 1 μV. For values up to about 1 μV the slope of the intensity function was just slightly less than unity.

Most investigators state that the slope varies with the frequency of the stimulating tone. Lower frequencies show a greater slope (14, 42, 83, 361, 390, 403, 404).

The limits of linearity or of constant slope of the intensity function vary with the kind of animal and with frequency. In each of the following instances the potentials were measured between the RW and neck. At low values in the pigeon where the slope is nearly unity the limit is about 1 μV (54). Wever and Bray (404) who worked with higher response levels and smaller slopes found the limits of constancy of this slope to be about 40 μV with the highest limit at about 60 μV. Mammals show a much higher limit. Covell and Black (83) found limits in cats at least as high as 140 μV with some as high as 400 μV. In their graphs Wever and Bray (402) draw straight intensity functions at least as high as 300 μV with one nearly to 700 μV. Wever and various co-workers (301, 392, 402) found that this limit is reached sooner with high frequencies than with low frequencies.

Bleeker and de Vries (44) recorded a maximum CM voltage in the pigeon of no more than 120 μV. Bray and

Thurlow (54) recorded an even lower maximum of 91 μV. Eyster, Bast and Krasno (143) report the largest response from any animal -- 20 mV from a guinea pig. More typical for guinea pigs and all other mammals tested (except man and monkeys) is the approximate value of 1 mV (273, 361, 392). The humans worked on had impaired hearing, at least to the extent that the eardrum had to be absent or severely perforated to allow insertion of an electrode into the middle ear. Even so, the maximum of 26 μV (14) or 25 μV (312) is surprisingly low. Lempert et al (281) state, in general terms, that responses from monkeys as well as humans are characteristically very low.

Maximum output is also influenced by the frequency of the stimulus tone. Maximum is reached at smaller response voltages with high frequencies than with low tones (14, 161, 164, 403, 431) and is rather constant for frequencies between 100 cps and 700 or 1000 cps (431). As mentioned previously, no true maximum was found for frequencies above 10,000 cps (431).

Differences of maximum values in the same species have been attributed to differences in efficiency of pick-up from a particular electrode placement than to true differences among cochleas (14, 44, 51). Davis, Riesco-MacClure and McAuliffe (118) mention differences in the maximum value of CM from various points on or in the same cochlea even though the intensity function has the same general form at all these points.

Davis et al (109) remark that nothing indicates that an all-or-none relation holds for CM as it does for the nervous response. The extensive linear growth with intensity seems to corroborate this observation. For every increase in intensity there is a proportional increase in the CM voltage. There are no stepwise changes. CM can follow the frequency of stimulation and apparently there is no recovery period needed after each cycle.

9. Threshold (AP).

Early determinations of thresholds for AP had to be made from total response patterns which included both AP and CM. Later, Davis, Gernandt and Riesco-MacClure (115) were able to view AP by itself in the guinea pig, at least for frequencies below 1000 cps by cancelling the interfering CM with electrical signals of the same frequency. They determined a threshold curve in decibels which falls linearly with the logarithm of the frequency from 150 cps or lower to at least 1000 cps. The slope of this function is about -28 db/octave in fresh preparations. Points beyond 1000 cps are uncertain but the total curve they constructed resembles the human threshold curve.

Galambos and Davis (165) found that there are different single neural units (second-order neurons) which are most sensitive to the same <u>frequency</u> yet which vary greatly in the minimum <u>intensity</u> required to stimulate them.

10. Threshold (CM).

Most of the investigators who tried to distinguish CM from AP say that the threshold for CM is very similar to the human audibility threshold (11, 104, 105, 108, 110, 247, 361, 362) and they say that the CM threshold curve runs parallel to but higher than the AP threshold curve (98, 105). Wever and Bray (392, 403, 410) claim that the CM threshold is that of the apparatus and they predict that no threshold for the animal will be found, i.e., they believe that when more sensitive recording methods are developed it will be found that CM will be seen in response to sounds at intensities below what is now regarded as "threshold."

Davis, Gernandt and Riesco-MacClure (115) show good indication that CM threshold is independent of frequency at least up to 5000 cps. Close similarities are shown between the conditioned reflex threshold and the CM threshold (104, 105, 360, 362) and McCrady, Wever and Bray (301) found reflexes of pouch-young opossum developing concurrently with CM in the frequency range which best brought out the reflexes. On the other hand, Dworkin et al (132) encountered enough inconsistencies between CM and conditioned reflex responses to question their parallel nature.

Wever and Lawrence (435), who used a wave-analyzer for a voltmeter, report the lowest CM response, 0.03 μV from a cat. Most others, using an oscilloscope to measure the threshold, have settled on a 1 μV response as an arbitrary "threshold" because lower values cannot be distinguished from

the baseline noise.

Lurie (294), Davis et al (111), Stevens and Davis (361), and Schuknecht, Neff and Perlman (351) attribute greater sensitivity to the external hair cells (EHC) than to the internal hair cells (IHC). CM "threshold" is elevated about 30 db when the external but not the internal hair cells are missing.

Black and Covell (42) point out that equal response contours for CM resemble human equal loudness contours. Stevens, Davis and Lurie (362) and Stevens and Davis (360) went even further by demonstrating that CM potentials of equal size are produced by the same relative stimulus strengths that give tones which sound equally loud to human observers. This problem has not yet been studied with pure CM from completely normal animals.

11. Latency.

There is no measurable latency for CM, at least none greater than 0.1 msec after the arrival of the sound at the eardrum (109, 122). This means that CM begins instantaneously (or almost) with the arrival of sound energy at the cochlea.

AP does have a delay, a minimum, at high intensities, of about 0.5 msec after the beginning of CM, before it appears in the oscillographic records (52, 98, 113, 126, 128, 361). This measurement (with a click stimulus) was usually made from the first negative peak of CM at the RW

to the foot of the AP spike. The change of latency with intensity is from about 0.9 msec at threshold to about 0.6 msec at approximately 30 db above the AP threshold (126, 127, 128, 361).

The latency of AP is shorter if the initial wave at the eardrum is a rarefaction instead of a condensation (99, 112, 113, 128, 201, 217, 336). This implies that the stimulating phase of the sound comes with an outward movement of the tympanic membrane and stapes. Gersuni (173) found no difference of latency with opposite acoustic polarities of the initial pressure wave. Neither did Davis, Fernández and McAuliffe (113) with the AP in response to an 8000 cps "tone-pip."

Derbyshire and Davis (127) measured the difference of latency for AP between a RW electrode and one on N VIII to be never less than 0.09 msec. Davis et al (116, 118) could find no difference more than 0.03 msec between the latency at the RW and other places in the cochlea, from base to apex. This was with a click stimulus.

Wever, Bray and Willey (426) claim that the nerve fibers discharge at a definite phase of the stimulating tone, at least for very low frequencies. Galambos and Davis (166) illustrate this for single units for frequencies up to 1050 cps and they estimate the upper limit of this phase correspondence to be about 4000 cps.

A later peak that appears in the record of the click response is also AP and is believed to be from the

homolateral cochlear nucleus (112, 113, 336). The time interval between this peak and that of the first AP is about 1 msec (112, 336).

12. Equilibration.

With a steady stimulus, AP from N VIII does not maintain the amplitude with which it first begins. Derbyshire and Davis (126, 128) and Stevens and Davis (361) describe a "fast" equilibration which is completed in 2 sec or less. Galambos and Davis (165) found that single neural elements reduce their original rate of discharge within a few tenths of a second and that there is a concomitant reduction in the size of each spike. They explain the "fast" equilibration by these two phenomena.

There is also a "slow" equilibration in the total activity of the nerve to an even lower output level (128, 361). This progresses from 5 to 7 min with continuous maximal stimulation. After the stimulus is stopped, recovery requires about 30 sec. This differs from fatigue, according to Davis et al (109), because a steady state is reached during which there is no further decline in responses with continued stimulation. CM shows no equilibration (109, 128), nor does AP from tone-pips pulsed at 20/sec (149).

13. Fatigue (AP).

Loud, prolonged sounds can permanently increase the thresholds of electrical responses or can reduce their amplitude for a given stimulus. When experimenters find the

impairment to be temporary they usually call it "fatigue." That AP does fatigue has been established, at least in a general way, by many investigators (32, 108, 219, 235, 303, 304, 336, 337, 341, 361). The amplitude during recovery at first overshoots the original normal value before it returns to that level (361). Rosenblith (336) found this to be true only for low tones. He observed no supernormal period for frequencies of 1000 cps and above. He also found that high-intensity clicks do not increase thresholds but he does report some supernormality with them. Fernández et al (149) report that tone-pips at 20/sec do not fatigue AP. McGill and Rosenblith (305) found no supernormality with clicks.

Hawkins and Kniazuk (219) give the most complete picture of fatigue as a function of intensity. With a masking noise at 50 db the rate of recovery does not depend on the duration of the white noise or on repetition. Recovery is slower with an increase of the intensity of the noise. Above 70 db, continued stimulation leads to cumulative impairment of the AP responses and the longer the exposure to the noise, the longer it takes for AP to recover. A 1 min exposure at 95 db temporarily eliminates AP while it reduces CM only slightly. Both components recover completely in 3 to 4 min. Rosenblith, Galambos and Hirsh (337) found that low-intensity test tones suffer more than stronger ones.

14. Fatigue (CM).

CM does not fatigue (108, 235, 337), at least with moderate intensities (110). Davis et al (109), looking at the total electrical response, noticed an occasional 10-15% reduction of CM during the first few seconds of a strong stimulus. Responses were maintained at this level. As mentioned before, Hawkins and Kniazuk (219) did find a temporary reduction of CM after 1 min of a 95 db level noise.

A phenomenon called "hysteresis" which Stevens and Davis (361) feel would be more aptly referred to as "overload" is described by them, by Galambos (162), and by Bleeker (48). The analogy to electromagnetic hysteresis can be seen by plotting the amplitude of CM as a function of the logarithm of the stimulus beyond the point where the responses fall off from their maximum. After prolonged supramaximal stimulation the intensity is reduced stepwise and the CM voltage measured. The curve so obtained does not fall on the original curve. It lies significantly below the original at all points. Complete recovery occurs after an interval which is longer for the more severe depressions.

Just as Rosenblith, Galambos, and Hirsh (337) found that AP suffers more for weaker test tones than for the stronger, Bleeker and de Vries (44) found that in the pigeon CM recovery is slower for <u>weaker</u> test tones after rather intense stimulation for 5 min by a pure tone of the same frequency as the test tone. In another series they found that a test tone of the same frequency as the fatiguing tone

(900 cps) shows a greater loss than a higher frequency test tone (1200 cps) when these test tones are intense. With weaker test tones recovery is longer for both but the 1200 cps tone shows a greater loss than the 900 cps test tone. In both sets of experiments the recovery time for the stronger test tones (the same level or 10 db weaker than the fatiguing tone) was less than 1 min. The weaker tones (at 30 or 35 db below the fatiguing tone) required 4 min or less to recover.

There is no reason to suppose that a different mechanism was fatiguing CM in each of the experiments described in this section. In each case it seems that fatigue was produced by overloading the structure(s) which was producing CM.

15. Inhibition (AP).

Galambos and Davis (165, 166, 167) observed depression of existing activity in single nerve cells when an "inhibiting" tone was given to the animal while another tone was stimulating. They also found that some tones suppress the normal spontaneous activity in the nerve. Low frequency tones were more effective inhibitors of the activity caused by high tones than vice versa but a fiber could often be inhibited by frequencies above or below the frequency which most easily stimulated it. Later, Galambos and Davis (168) discovered that their single units were cells of the cochlear nucleus and not first-order fibers of the

auditory nerve as they first believed. Therefore, inhibition at the cochlear level is not proved, nor disproved.

16. Interference (CM).

Covell and Black (83), Wever (391), and Wever, Bray and Lawrence (419) claim that CM response to a given tone can be reduced by the simultaneous presence of another tone. This "interference," so similar in principle to masking except that tones of any frequency can interfere with any other tone, occurs only when the interfering tone is of high intensity (83, 419). After removal of the interfering tone there is depression of responses, sometimes permanent (419). For these reasons interference of CM cannot be considered as clear a phenomenon as masking. The effects are not distinct from those of "overload" or "hysteresis." The earlier observations of Davis and Derbyshire (103) and of Stevens and Davis (361) that CM from separate tones do not interfere but merely add algebraically, can still be trusted at moderate intensities.

D. Responses During Death, Anoxia, and Circulatory Failure

The general pattern of the change of electrical responses with death, anoxia, or interference with circulation that leads to death is this: AP disappears almost at once (32, 33, 61, 122, 289) and CM falls to a low, gradually decreasing level (10, 61, 122, 290, 395, 402).

Davis et al (109) describe the time course of the initial drop in CM merely as "prompt" and Juul (247) and

Seymour and Tappin (353) say that the drop occurs "immediately" with death.

In more specific terms Bast et al (31) say that the drop comes within 5 min after cessation of circulation. Lurie (293) says that CM falls to its post-mortem level "within a minute or so" and Stevens and Davis (361) say that this level is reached in 2 or 3 min.

The graphs in a paper by Wever, Bray and Lawrence (423) show that the beginning of this rapid drop is usually well within 5 min after cessation of respiration or interference with circulation to the ear. This rapid drop is usually completed in about 5 min. Harris et al (213) found this initial sharp drop to end in about 7 to 9 min, with a range of 6.25 to 11.00 min. Bornschein and Krejci (51) paid particular attention to the time course of this decay. In 3.2 ± 0.9 sec after they tied the aorta, the drop began. After 30 to 60 sec there was a noticeable decrease in the rate of the fall and after 90 to 120 sec the response gradually fell to the post-mortem level.

Wever et al (432) subjected cats to low concentrations of oxygen and followed the accompanying changes in the level of CM. The animals did not die and the changes were slower than those just mentioned. The steepest part of the drop came after 10 min of breathing the gas mixture. From the graphs it seems that the end of the drop comes at 18 min for an animal breathing a mixture containing 0.75% oxygen and in less than 31 min for a cat breathing a mixture with 3%

oxygen. Wever and his group made histological studies of some of the animals used in these experiments and found general degeneration of the organ of Corti (OC) with the external hair cells (EHC) damaged more than the internal hair cells (IHC). In a later study (274) Lawrence and Wever found that the first sign of degeneration of the hair cells occurs at the base of the cells.

The initial drop has been described as a rapid decrease in intensity (31), a fall to a lower level (110), a drop in level (161, 162), a decrease (396), or a prompt fall to the post-mortem level (109). Harris et al (213) mention a minimum level of 10-12 μV, but this is not particularly informative because, in this abstract of a longer paper, they do not give the original level or the stimulus strength. Juul (247) and Seymour and Tappin (353) talk of "a relative drop to 1/5 of the original level" and Lurie (293) and Stevens and Davis (361) say that the response fell 80% or more.

The values calculated from Wever, Bray and Lawrence's graphs (423) of the amplitude of the potential as a function of time after death (constant stimulus strength) cluster closely around 14 db loss (range of 10 to 18 db). The CM losses ranged from about 15 μV to 760 μV from starting levels of 18 μV to 850 μV. The graphs of Wever et al (432) for the animals breathing gas mixtures deficient in oxygen show (by the present author's approximations) a drop to 180 μV from 247 μV, or less than 3 db, for

"rebound" the most thorough investigation. They found it to be a common feature regardless of how the cat or guinea pig was killed. The peak of the rebound occurs anywhere from 5 to 12 min after the beginning of the initial rapid drop. It occurs in the absence of the middle ear muscles, which eliminates the effects of the intraural muscles as a possible cause. Wever, Bray and Lawrence offer no explanation for the phenomenon. The rebound will be discussed further in Chapter V.

Galambos observed the same phenomenon in bats which were being stimulated with intense tones of frequencies up to 55 kc. He noted a rebound 2 to 4 min after "death" (161) and 5 min after cessation of respiration (162). His explanation is a breakdown of the protective reflexes of the intraural muscles because of asphyxia of the central nervous system. The lack of rebound in previously curarized animals led to his conclusion. However, Galambos himself (162) found an irreversible decrease of CM with curare even before death. In the Wever, Bray and Lawrence paper (423) the graph of the death function with curare shows the smallest initial loss and a long plateau rather than a rebound and in a later paper (274) Lawrence and Wever show that curare damages the organ of Corti severely. The absence of rebound following death after curare has been given to an animal is probably attributable to partial loss of CM even before death (see Chapter V), so that Wever, Bray and Lawrence are probably correct when they infer that the intraural muscles

are not involved in the normal "rebound."

The graphs in the paper by Wever et al (432) about CM in anoxic cats can also be interpreted to show a rebound after the initial drop. In an animal breathing the 3%-O_2 mixture the peak of the rebound comes at 50 min after the cat began to breath this mixture and at 18 min after beginning to breath the 0.75%-O_2 mixture.

Bornschein and Krejci (51) report an "S-shaped" course of the initial potential loss during their preliminary experiments when they killed the animal with chloroform. This may indicate a rebound but it is impossible to say with any certainty without seeing the curves or raw data. They failed to get this S-shaped course when the animals were hypoxic before they were killed.

By direct statement, by their inferences, or by what can be inferred from their statements, practically all authors who have written about the loss of potentials during death, anoxia, or circulatory difficulties attribute the loss to a lack of oxygen (46, 47, 48, 50, 51, 109, 116, 122, 126, 213, 222, 335, 353, 423, 432, 445). Some of these have shown the CM loss to be independent of blood pressure (48, 423). Gisselsson (184) claims that there is a dependence. Losses have occurred often before cessation of the pulse or heartbeat (122, 335, 432). Bornschein and Krejci (48) showed that losses can take place with circulation intact if anoxic blood is substituted for the animal's normal blood. Harris

et al (213) have shown that CM losses are not due to carbon dioxide.

Seymour and Tappin (353) found that stimulation of the cervical sympathetics brings about a partial loss of CM, presumably by affecting the circulation to the ear. The authors' inference is that the direct cause of the loss is lack of oxygen, with circulatory interference bringing about this deficiency.

The method of killing the animal does not influence the general changes of CM with death (423). However, Wever does point out (392) that a violent form of death produces more severe and rapid losses than a slow and easy death. Tying the aorta causes a more rapid reduction of CM than is caused by any other method (51, 423). Bast et al (31) also state that disappearance of CM response is quicker with more rapidly acting poisons.

Bornschein and Krejci (47) and Wever, Bray and Lawrence (423) found that changes with death are independent of the degree of stimulation of the ear. Wever and his co-workers (392, 432) qualified this with the stipulation that the intensity must be held below the level of physical injury. In another study (445) it was found that hypoxic animals show no loss of CM as long as breathing and circulation continue but that loss from exposure to loud noises comes quicker in these animals than in the normal control animals.

Bornschein and Krejci (47), Hallpike and Rawdon-Smith (206), and Wever et al (432) found that changes with death

take parallel courses at all frequencies of stimulation. In one animal with an original severe loss at 4000 cps, Bornschein and Krejci (49) found that CM at this frequency took the same course with death. Wever, Bray and Lawrence (423) did find some differences in the later parts of the decay. High tones usually declined more rapidly. In this same study they found no relation between temperature and initial CM loss but when they applied heat during the decay of the post-mortem potentials there was a noticeable increase in amplitude.

Many of the graphs of the amplitude of potentials versus time (423) show a small rise in CM before the sharp drop with death. Here, relaxation of the intraural muscles may really be responsible. Seymour and Tappin (353) sometimes detected a small increase of CM after stimulation of the cervical sympathetic trunk, before CM decreased below its original starting level. This preliminary increase was never more than 1/8 of the original value.

Bornschein and Gernandt (46) and Davis and his co-workers (116) found the effects of anoxia on AP to be completely reversible if the oxygen deprivation was not too long or severe but successive exposures of the animals to anoxia accumulated the damage so that some permanent impairment of AP was produced (46).

There is also complete restitution of CM if anoxia is not carried too far (46, 51, 116, 184, 213, 361, 395). CM recovers only partially if anoxia is prolonged or too severe (50, 184, 213, 335, 353, 432). Repetition of the

anoxic condition leads to accumulated losses (274, 353, 432). Bornschein and Krejci encouraged partial recoveries by exchanging anoxic blood for blood from a normal animal (48) and by perfusing the animal with solutions containing oxygen (50).

Post-mortem responses, i.e., those after the initial drop in CM during death or anoxia, differ only in amplitude from ante-mortem activity (361, 423). The form of the intensity function remains the same (423). Bornschein and Krejci (47) show that the slope of the intensity function is almost unity up to about 100 μV. Their two graphs indicate a long bending from the straight line portion starting about 20 db below the maximum amplitude.

Buitendijk (61) noticed an increase in the latency of AP with death of his animals. Bornschein and Gernandt (46) claim that anoxia delays the beginning of AP.

E. Nature of Responses - Abnormal

1. Drugs and Chemicals:

Davis and Saul (122) found CM resistant to narcosis. Specifically, they state, with Derbyshire and Lurie (109), that ether anesthesia reduces CM output very little. Bleeker (43) noticed no change with urethane given intraperitoneally. Saul and Davis (348) found AP less resistant than CM to anesthesia.

With direct application of novacaine to the auditory nerve, Bast et al (31) and Davis and Saul (119) eliminated AP without disturbing CM. Davis, Gernandt and

Riesco-MacClure (115) eliminated AP by intramuscular injections of quinine dihydrochloride.

Most procedures were not aimed at altering AP, at least as a prime target. The experimenters tried to alter CM and chiefly by placing toxic materials or ordinarily innocuous materials in toxic quantities on the round window (RW). They used NaCl more frequently than any other one substance.

Adrian, Bronk and Phillips (10) produced no change in CM with NaCl but everyone else who reported using the salt did alter CM. Eyster, Bast and Krasno (143) and Hallpike and Rawdon-Smith (206) state, in a general way, that NaCl on the RW does damage the CM response.

The course of depression of CM by NaCl follows a pattern similar to that during death and anoxia. Hughson, Thompson and Witting (237), Wever and Bray (407), and Walzl (376) describe an initial increase in responses which Walzl says amounts to 5 db before CM begins falling. Wever and Bray describe the ensuing loss as "rapid." This is followed by a gradual decline.

Fowler and Forbes (155, 157) state that the loss is a function of the time that the salt remains on the RW. Wever and Bray (407) add that it is also a function of the quantity of salt applied. In their paper, the graphs show a median loss of CM of about 75 μV, or about 11 db.

With application of NaCl on the RW, Covell and Black (84) found high-frequency responses affected earliest,

and Fowler and Forbes (156) found them most severely damaged. Wever and Bray (407) and Walzl (376) agree, generally, that the initial steep loss is about the same for all frequencies but that the secondary loss is more severe for the higher frequencies. They also agree that the impairment is greater and earlier at an electrode in the region (apex or RW) where the NaCl is applied.

Just as with death and anoxia, the intensity function maintains its slope and shape for high frequencies after treatment of the cochlea with NaCl (407). The low tones show a slight reduction in slope. All the curves are displaced to greater values on the intensity axis (84).

Fowler and Forbes (155) say that there is no recovery with NaCl or with any of the electrolytes they used. Wever and Bray (407) report partial recovery in some cases, followed by a further decline in CM. The recoveries in these less severe cases were about 10 μV.

Fowler and Forbes (155) report increases in thresholds for conditioned reflexes in dogs when CM is affected. They also found (156) that the conditioned reflex responses are affected more for high tones than for low tones when NaCl is put on the RW.

Histopathology reveals that NaCl on the RW attacks the basal end of the cochlea first, according to Fowler and Forbes (156, 157). They also relate (156) that the external hair cells (EHC) suffer more than any other cochlear component and that when the EHC show any damage the external sulcus

cells are also affected. They found no evidence that there had been constant pressure on any of the membranes which divide the cochlea into separate channels or on the RW. Covell and Black (84), on the other hand, report rupture of the basilar membrane and Reissner's membrane by large changes in osmotic pressure.

Walzl (376) found that KCl produces the same changes as NaCl but more speedily and severely. This similarity proves important in later discussion (Chapter V) because it can be assumed that KCl produces the same type of histopathology that NaCl produces.

Eyster, East and Krasno (143) effected no changes in CM with many of the agents placed on the RW: choloroform, nicotine, nupercaine, alcohol, formaldehyde, and glucose crystals. Covell and Black (84) found 95% alcohol almost without effect. In fact, when they placed the alcohol on the RW before applying crystals of $MgSO_4$ or NaCl, they reduced the damaging action of the salts. Fowler and Forbes (157), not surprisingly, found physiological NaCl or pure H_2O to have no effect on CM.

Other things reported as damaging to CM when applied to the RW are: cocaine (10, 109, 206), $CaCl_2$ (155, 156, 157, 376), glycerine (155, 157), quinine dihydrochloride (143, 155, 157), $MgSO_4$ (84), "quinine" (190), and nicotine (190). This last reference is in contradiction to the findings of Eyster, East and Krasno discussed in the previous paragraph.

It can be concluded from all of these reports that: (1) electrolytes on the RW produce more damage than non-electrolytes, at least more permanent damage, and (2) KCl is the most effective agent of those described.

Walzl (376) produced damage to CM by perfusing the cochlea with various fluids. His three principal conclusions are: (1) the injury done is equal for all stimulus frequencies, (2) each agent works with a different speed and extent, and (3) great changes in the hydrogen ion concentration have very little effect on thresholds. Perfusing with cerebrospinal fluid caused no damage.

Here are some interpretations of the effects described in this section. Wever and Bray (407) explain the preliminary rise in CM with application of NaCl to the RW by better electrical conductivity to the electrode. They attribute the initial rapid loss to changes in pressure relations and the final gradual decline to progressive impairment of the hair cells. Hughson, Thompson and Witting (237) suggest as a possibility that the early increase comes from temporary fixation of the RW because of changes in pressure (which they believed could improve the responses) before the salt poisons the cochlear structures. Walzl (376) concludes that the loss of CM by introduction of chemicals into the cochlea is caused by chemical action and not by changes in osmotic pressure. Covell and Black (84) feel that NaCl produces greater damage than $MgSO_4$ because NaCl ionizes to a greater extent.

Many experimenters injected chemicals into the general system of animals and observed the changes of the electrical responses of the cochlea. Juul (245) and Juul and Vraa-Jensen (249) saw no effects with salicylic acid, allypropanol, adrenaline, prostigmine or calcium. Large quantities of physiological saline injected intraperitoneally gave no changes and more concentrated NaCl solutions caused irregularities but not reductions in CM. Juul and Vraa-Jensen (249) did find that chronic ascaridole poisoning depressed CM depending upon the extent of damage to the organ of Corti (OC). The drug attacked the basal and apical turns earliest and most severely. The hair cells deteriorated earliest with the EHC showing earlier and greater damage than the IHC. Ascaridole did no particular damage to the nerve cells.

Galambos (162) noticed that curare injected into a bat lowered the CM level after a while, 23 min in one case. CM never regained its original magnitude. Galambos could not account for the effect.

Caussé et al (70) injected a drug, arsacétine, into a guinea pig and produced deafness, measured by Preyer's reflex, in about 6 hours. There was always loss of CM.

Hawkins (218) used streptomycin which, he inferred, damaged the hair cells. AP decreased, but a curve of the voltage output (linear) versus the logarithm of the stimulus shows the same slope as AP from a normal animal. At high

intensities there is a dip in this curve followed by a regrowth with a slope equal to that in the normal pattern. Hawkins remarks that the maximum response of CM is reduced but that the lower level responses are not very different from the normals. However, the intensity function (logarithm of the CM voltage versus the logarithm of the stimulus strength) shows a smaller slope which is significantly different from the normal. In two greatly affected ears the entire CM pattern in response to a click did not reverse completely when the initial sound wave at the eardrum was changed from a rarefaction to a condensation, or vice versa. (In the normal animal, the polarity of CM reverses with such a reversal of acoustic polarity.) Christensen et al (80) found that streptomycin given in large quantities to guinea pigs produced severe deafness but did not alter CM. The authors conclude that streptomycin does not affect the hair cells.

Gisselsson (184) is the only author to report an increase in the latency of CM. He detected a slight delay of CM in his oscillographic records relative to the normal time of its appearance. This occurred with the injection of physostigmine into the animal or with acetylcholine in the presence of an anticholinesterase. He argued (not entirely convincingly) that this change occurred in the inner ear and was not due to changes in the intraural muscles.

2. Acoustic Trauma.

Permanent damage from excessive acoustic stimulation, acoustic trauma, has been a favorite tool for many years in the study of auditory function. Since 1930 many investigators have written of changes in the electrical responses of the cochlea after acoustic trauma. Most studies were done with pure tones. Davis et al (104, 105) and Wever and his co-workers (414, 438) found that the frequency whose CM response suffers most is not necessarily the stimulus frequency. Covell and Black (84) and Smith and Wever (356) noted loss not only for the stimulating tone but to some degree for all frequencies. Caussé and Chavasse (73) found a slight indication that the maximum loss may occur at the stimulating frequency. Rüedi and Furrer (345) noticed the greatest damage at frequencies above that of the stimulating tone but losses to some extent for practically all frequencies. For tones 6000 cps or above they observed losses only for frequencies above 4000 cps (346); in general, they found 4000 cps the most susceptible frequency.

Covell and Black (84) say that pure tones cause injury at intensities just beyond those at which CM reaches its maximum. Wever and Lawrence (427) say damage is produced beyond this maximum of the intensity function but also note (431) that some ears show effects of stimulation at levels below that which produce maximum CM. Fernández et al (149) quantify this factor for an intense 9000 cps stimulus. They calculate that damage occurs whenever the product of the

sound pressure in dynes per square centimeter and duration of the stimulus in seconds is greater than 30,000.

Other intense sounds produce variable damage to the cochlear potentials with the responses to 4000 cps seemingly the most vulnerable.

Even after acoustic trauma the shape of the intensity function does not change much. According to Wever and Lawrence (427, 431) the slope is still unity or slightly less. They also found (431) that to reach the maximum a higher intensity is needed. They interpret this to mean that all the cochlear elements had not been called into action at maximum in the normal animal. Bornschein and Krejci (53) note that the smaller responses after acoustic trauma can be restored nearly to the pre-exposure amplitude and pattern with increase of the strength of the test tone. Both CM and AP change equally, in damage and in restoration.

Recovery from acoustic trauma has not been studied extensively. Alexander and Githler (12) exposed guinea pigs to jet engine noise for 15 minutes and observed reduction in CM from normal levels. They noticed progressive partial recovery up to about three weeks after the trauma but further degeneration followed this. In another study it was found that when acoustic trauma is superimposed on hypoxia (145) responses to low intensity test tones suffer more than higher intensity responses and they recover more noticeably. Fernández et al (149) saw occasional slight recovery when the product of the sound pressure and duration of stimulus was less than 30,000 (see above).

Alexander and Githler (12) note the great susceptibility of traumatized ears to further trauma, even by moderately intense sounds. Wever and Lawrence (431) also remark about the cumulative effect of traumatic injuries, even very small ones.

Those who have made histopathological examinations of traumatized ears agree to these findings: (1) EHC are always the first cochlear structures to be clearly injured, usually in the cochlear region predicted from the frequency showing the greatest CM loss, and (2) there is never any IHC damage without damage to the EHC (13, 104, 105, 193, 220, 269, 294, 300, 308, 347, 351). Davis, Lurie and their co-workers (111, 294, 362) state, with only moderate restrictions on their certainty, that the loss of the EHC leads to an increase of CM threshold of about 30 db. Schuknecht, Neff and Perlman (351) claim that the loss of EHC only results in a 40 db loss. At first, Davis and his co-workers (111) found good but not exact correspondence between CM, conditioned reflexes and histopathology. In a later investigation (132) some of these same authors found practically no correspondence of these factors.

3. Surgical Trauma.

Cutting N VIII abolishes AP within a few days but has no effect on CM over a period of weeks. CM also suffers if circulation to the cochlea has been interrupted (1, 194, 195, 196, 238, 291, 331, 437). The Ashcroft, Hallpike and

Rawdon-Smith group disagreed with this usual observation (28, 197, 206, 208) because they had many cases of no CM with normal or nearly normal CC, and only degenerated neural elements. But later, Rawdon-Smith with Hawkins and Lurie (331, 332) performed careful sections of N VIII and found normal CM without any AP.

Rawdon-Smith, Hawkins and Lurie (332) found that maximum CM voltage was not affected by total section of the nerve. Wever and Neff (437) saw no change in the intensity function after partial section of N VIII. Whenever there was some loss of CM it was never as great as the threshold losses determined by conditioned reflexes.

Wever and Bray in their classic first paper (394) state that the responses which they picked up from N VIII disappeared after destruction of the homolateral cochlea. Van Gilse (182) noticed reduced responses from the cochlea after he made some holes in it. With microscopic examination he found physical injury to the sensory structures.

Hughson and Crowe (232) note that rupture or puncture of the RW results in great loss of electrical responses for all frequencies. Davis et al (109) detected an <u>increase</u> of the recorded response with just a small puncture of the RW. They attribute the improvement to a decrease in the electrical resistance. Guttman and Barrera (196) noticed no loss in cochlear responses with perforation of the RW but they destroyed the response completely by chipping off the bony rim of the RW.

Actually entering the cochlea has provided variable results. Guttman and Barrera (196) removed tiny quantities of perilymph with a hypodermic needle and caused no change in the cochlear responses. Eyster, Bast and Krasno (142) made holes in the bony cochlea without breaking the endothelial lining and caused very little reduction. Davis, Riesco-MacClure and McAuliffe (118) found that small holes which allowed fluid to escape, in time caused small losses in both CM and AP. Riesco-MacClure et al (335) noticed very little change for several hours in the response from a RW electrode to a 1000 cps tone after considerable surgical damage including cutting off the two apical turns.

Eyster, Bast and Krasno (142) observed that serious loss occurred with opening of the cochlea but that there was gradual recovery. In the same paper they report complete loss or at least severe reduction of low frequencies from amputating the two apical coils. In a later paper (143) they say that opening of scala media alone caused prompt and complete loss of CM. They make no mention or suggestion of recovery. Guttman and Barrera (196) found that bleeding in any of the scalas also produces considerable damage to CM.

Injury to parts of the vestibular system can cause reduction or complete loss of cochlear responses. Fromm, Nylén and Zotterman (159) and Lowy (290) report losses with opening or puncturing the membranous semicircular canals, Wever (387) with damage to the vestibule, and Adrian, Craik and Sturdy (11) with opening of the saccule.

Davis et al (116) observed that CM can show local losses with localized cochlear injuries that do not necessarily involve the organ of Corti (OC). Eyster, Bast and Krasno (142) explain the effects of surgical trauma as disturbances of normal pressure relations. Considerable increases in the hydrostatic pressure by increasing the cerebrospinal fluid pressure (91, 270) reduce CM somewhat but Krejci and Bornschein (270) attribute this to pressure on the blood vessels, thereby interfering with the vascular supply. Increasing the pressure on the cochlea, either by increased air pressure in the middle ear (425) or by pressure on the RW (108), has little or no effect on CM except for loss of sensitivity because of alteration of the sound transmitting system (425).

Kobrak and his co-workers (131, 261, 262) eliminated the middle ear reflexes by making holes in the cochlea, but did not eliminate CM.

4. Electrical Polarization.

Wever and Bray (386, 395, 396) first reported the effects of a polarizing current on cochlear responses. Application of direct current of either polarity to N VIII blocked the responses. Responses returned when the direct current was removed. Wever and Bray thought that the direct current might have set up a conduction block by electrotonus (395). Eyster, Bast and Krasno (144) obtained changes in CM

from a strong polarizing current through the cochlea only after electrolysis had caused considerable physical damage. Fernández et al (148) tell a similar story. They used direct current, alternating current of 1000 cps, and radio-frequency current but produced no changes in the electrical responses until heating damaged the cochlear tissues or until bubbles from electrolysis or heating interfered mechanically. Histopathological examination showed that EHC suffered more than anything else. Often, with very weak direct current polarization some reversible depressions in CM and AP were produced.

Tasaki and Fernández (366) avoided electrolysis by polarizing through glass capillary electrodes filled with agar-ringer gel. They found that AP, CM and summating potential (see Section H) are all increased when the source of direct current flow is in scala vestibuli and the sink is in scala tympani. All the potentials are decreased when the direction of flow is reversed.

5. Temperature.

Derbyshire and Davis (127) determined, by inference, that there is a decrease in the maximum frequency of synchronization of the nerve fibers with the stimulus frequency when the fibers are not maintained at normal temperature. Adrian, Craik, and Sturdy (11) also observed a decrease in the upper limit of synchronization of AP in cold-blooded vertebrates with a decrease in temperature.

Kahana, Rosenblith, and Galambos (250) made the most extensive study of temperature effects. They used the hamster, which lives at a reduced metabolic rate during prolonged exposure to cold and is restored to normal activity when the temperature is returned to normal. The authors found that AP begins decreasing when the temperature of the hamster is dropped below 30°C. AP decreases more rapidly than CM and disappears at temperatures at which CM is still present. The greater the stimulus intensity, the lower the temperature has to be before AP disappears. They found that for a given temperature there is a greater voltage while cooling than while warming. They also noticed that for a given temperature there was a greater latency during cooling of the animal than during warming. The latency, too, begins increasing as the temperature decreases below 30°C. The clearest effects are in the range of 25°C to 18°C.

Adrian, Bronk, and Phillips (10) first noticed that cooling weakens CM. Responses return to normal provided that circulation has remained intact; otherwise, potentials decline from their cooled level. Fromm, Nylén and Zotterman (159) claim that heating increases CM. No one else has made a similar claim for normal animals. Adrian, Craik, and Sturdy (5) say that increases of temperature in cold-blooded vertebrates has little effect on CM. Wever, Bray and Lawrence (423) noticed appreciable increases in CM of the post-mortem responses with temperature increases.

CM suffered in the same temperature ranges as AP in the study by Kahana, Rosenblith and Galambos (250). CM begins decreasing as the temperature drops below 30°C and shows the most definite effects between 25°C and 18°C. CM declines more slowly and persists longer than AP. There is no change in the latency for CM. The authors found that these changes are essentially reversible for both CM and AP.

6. Pathological Animals.

Some animals are born with a pathological involvement which attacks the ear as well as a few other restricted portions of the body. Of these, albinotic cats have been studied most extensively. That these animals which were tested gave no CM or AP was stated unequivocally by Davis et al (108), by Howe and Guild (228, 229), by Hughson, Thompson and Witting (237), and by Lurie (293). Lurie, Davis and Derbyshire (299) found just a little CM and no AP in a cat which appeared deaf and was probably albinotic. Howe (228) never obtained electrical responses from an animal which appeared "clinically deaf."

The histopathology described for animals in these experiments varies considerably but all findings contain in common a partial or complete degeneration of the organ of Corti (OC). Atrophy or collapse of the saccule is mentioned in most cases. Other things mentioned as being affected are the stria vascularis (108), and N VIII and the spiral ganglion to varying degrees (228, 229, 293).

Lurie studied the waltzing guinea pig extensively (293, 295, 296, 297). He seldom found any electrical responses except occasionally some CM for low frequencies at very high intensities, and in those cases there was always some segment of normal OC in the region corresponding to the frequency of the obtained CM. In most of the waltzing guinea pigs there was partial or complete degeneration of the OC. Lurie traced the course of degeneration which he found began with the hair cells, then spread to the remainder of the OC, and then to the spiral ganglion. He found the basal turn to be the earliest section of the cochlea attacked.

The shaker-1 mouse whose pathology resembles that of the waltzing guinea pig gives abnormal CM (191). The frequency impairments correspond to appropriate regions of degeneration of the OC, e.g., a high tone loss matches degeneration in the basal turn. Grünberg, Hallpike and Ledoux (191) found these degenerative changes to be progressive with age but they found no abnormality in Reissner's or the tectorial membrane, or in the vestibular apparatus.

Hughson, Thompson, and Witting (237) got no electrical responses from deaf Dalmatian puppies. Lurie's histopathological studies of deaf collie and Dalmatian dogs (298) show gross changes in the collapsed cochlear duct, including degeneration of the OC.

In general, Stevens, Davis and Lurie (362) found no CM from deaf animals; Davis, Derbyshire, Lurie and Saul (108) recorded no CM from an animal with labyrinthitis, and

in one animal (109) with a normal OC but affected spiral ganglion they detected CM but no AP.

Bast and Eyster (30), Eyster, Bast and Krasno (142), and Hallpike (201) describe findings out of line with the general nature of those described for pathological animals. They report normal or nearly normal CM with extensive degeneration of the OC.

F. Microphonics from the Vestibular System

Pumphrey (320) first described a clear-cut microphonic from the utricle. Lowenstein and Roberts (283) and Huizinga, de Vries and Vrolijk (240) verified the microphonic potentials in later experiments. Zotterman (444) observed "saccular microphonics" which he believed were generated in the saccular macula.

Sound stimulation may also evoke a microphonic response from the semicircular canals of pigeons. The responses are truly vestibular because they are elicited after the cochlea has been extirpated.

Bleeker (43), de Vries and Bleeker (372), and van Eyck (134, 136, 138) all state that a semicircular canal has to be fenestrated before microphonics can be elicited. Van Eyck (134) adds that the eardrum and middle ear must be intact. He was able to pick up these responses with an electrode anywhere in the middle ear.

Van Eyck (134) defined the range of microphonic responses as 200 to 3000 cps. He, and also de Vries and Bleeker (372), state that these microphonics have the same

general shape as CM, i.e., they reproduce the pattern of the acoustic stimulus. However, de Vries and Bleeker say that for pure-tone stimuli these microphonics vary more from the sinusoidal form than does CM.

Van Eyck (134) says that the polarity of the microphonics from the semicircular canals is opposite on opposite sides of the ampullar crista. De Vries and Bleeker (372) found no difference and conjecture that the microphonic voltage is generated between the top and bottom of the crista. Van Eyck (136) has observed a reversal of the microphonic polarity with reversal of the polarity of the acoustic click. The accompanying AP spike does not reverse.

De Vries and Bleeker (372) plotted the logarithm of the microphonic voltage against increases of the stimulus intensity in decibels and found a slope which approached unity only at low intensities. However, the amplitudes were not lower than the CM output from the cochlea under the same conditions.

Van Eyck (136) detected no latency for microphonics. AP does show delay and it begins sooner if the original movement of the endolymph is in the proper stimulating direction according to Ewald's laws.

Van Eyck (138) also studied the effects of fatigue which are chiefly the depression of the amplitude of AP and the prolongation of its latency. The microphonic also decreases after prolonged stimulation but not so much as AP

does. A short interruption of the fatiguing sound restores all the patterns to normal. Under the same conditions CM from the cochlea does not change appreciably. Van Eyck says that the microphonic from the semicircular canals fatigues with continuous stimulation by sound because the semicircular canals are subjected to a stimulus which is not natural for them.

Van Eyck found that asphyxia removes AP leaving the microphonics from pure tones more nearly sinusoidal (136). Cocaine removes all responses and cooling depresses or abolishes them (134). Effects of quinine are like those described for fatigue and are additive with the effects of fatigue. Bleeker and de Vries (43, 372), and van Eyck (134) all report the disappearance of the microphonic responses with destruction of the ampulla from which the electrodes are detecting the responses.

Van Eyck (135, 137, 141) reports another phenomenon which no one else has even alluded to, before or since. He produced oscillating potentials (frequency from 800 to 1200 cps, about 50 μV) by exerting "continuous" pressure by an air jet on an ampulla of a semicircular canal. He observed the oscillating potentials in each canal provided the movement of the endolymph was in the proper stimulating direction according to Ewald's laws. The pressure was not strong enough to elicit cephalic nystagmus. The responses persisted in curarized animals but cocaine and death abolished them. They persisted for a short period during anoxia. Van Eyck

proposes two possible explanations for the phenomenon: (1) pressure brings about an oscillatory movement of the endolymph, or (2) some automatic depolarization process, enhanced by the pressure, takes place in the sensory cells of the crista. This phenomenon cannot be regarded seriously until it can be repeated in a pigeon whose eardrum and columella have been removed, and with the continuous pressure exerted by a shock-mounted rod. It is very possible that in Van Eyck's experiments resonant frequencies of the middle ear and the cavities produced by the operation were excited by the mixed noise of the air jet and stimulated the semicircular canals acoustically.

G. Origin and Significance of CM

1. Origin of CM.

For this discussion two points will now be accepted as adequately proven by the evidence presented: (1) AP arises from the neural elements of the ear and has the same properties as action potentials from any nerve of the body, and (2) CM is a biological phenomenon and not an artifact.

Evidence from the previous investigations leans undisputedly to the hair cells of the organ of Corti as the structures responsible for the production of CM. None of the other possible structures received much support after 1937. The evidence favoring the hair cells can be found in the sections concerning deaf animals with congenital or other pathological involvements, acoustic trauma, effects of chemicals, sectioning of N VIII, and anoxia. The one factor

clearly correlated with CM depression is damage to the hair cells. Where it was possible to detect degrees of damage, the EHC were affected earlier and more severely than the IHC. Serious loss of CM usually corresponded to extensive degeneration of the OC and other structures within scala media.

Those who favor the hair cells as the seat of the CM response agree almost unanimously that CM is caused by distortion of the hair cells (68, 106, 107, 109, 194, 211, 251, 360, 361, 392, 403, 431, 432). Most of the authors say directly or else imply that the hair cells behave like piezo-electric crystals because with distortion they generate potentials of opposite sign at their opposite ends, much the same way that piezo-electric crystals do when they are compressed. The comparison really has been to the results of piezo-electric action and nowhere in the literature is there even speculation that the hair cells may behave like piezo-electric crystals because they have the same physical structure. Wever's speculative interpretation (392) is that the positive field on the outside of the hair cell membranes is strengthened or weakened by synergic push-pulls on the cell and hair tufts, which action supposedly changes the permeability of the cell membranes thereby allowing the negative charges inside the cell to exert a lesser or greater influence on the positive charges outside. This explanation does not account, without some further hypothesis, for the opposite electrical polarity of CM on the opposite sides of the basilar membrane.

Jielof, Spoor and de Vries (242) infer from their experiments on the lateral line organ of the fish that the cochlear microphonics, as well as the microphonics from the vestibular system and the lateral line organs, are the results of tension on the hairs of the hair cells. This hypothesis appears quite tenable.

Wever and Lawrence (393, 435) argue against pressure itself as the adequate process for generating CM potentials. Their thesis is that when a stimulus is in phase at both oval and round windows there is a maximum of pressure exerted on the cochlear partition. Actually, in this situation CM is at a minimum. There is a maximum of CM with 180° phase difference at the windows.

Another concept, unchallenged until Békésy's paper on the energy balance of the cochlear partition (38), is that the source of energy for CM is the sound wave and that the hair cells merely convert the mechanical energy into electrical energy (99, 194, 211, 251, 360, 361, 392, 403, 431, 432). Békésy contends that some of the energy for the microphonics is contributed by a "chemical-energy pool" within the cochlea. Békésy's calculations are based on several approximations and in the single example that he illustrates the difference between the mechanical energy imparted to the cochlea and the electrical energy dissipated is not large enough to be impressive.

2. Significance of CM.

The general agreements so far discussed cease with the interpretation of the significance of CM. One extreme contends that CM actually stimulates the nerve (53, 98, 106, 107, 109, 194, 247, 249, 299, 334, 392). The other extreme believes that CM is an epiphenomenon, i.e., that it may indicate that something is going on in the ear but that it has no auditory function (4, 214, 251, 353). Caussé (65) and Davis and his group (115, 116) say specifically that CM does not stimulate the nerve endings.

Those who contend that CM does not stimulate the nerve assign that function to a chemical effect (57, 127, 128, 157, 254) with a likelihood that acetylcholine is the specific agent (361). Wever (390) speaks out against chemical mediation for stimulation of N VIII.

Another category of opinion is that CM parallels auditory function (43, 45, 64, 83, 92, 95, 97, 151, 269, 312, 362, 380, 382). Specifically, Juul (246) and Lurie (296) say that there is no CM with absence of the pinna reflexes or any other indication of deafness in guinea pigs. Stevens and Newman (364) found that the slope of the loudness function is just slightly less than the slope of the intensity function for CM. Adrian (9), Davis et al (111), and Howe (228) point out that both CM and hearing depend on the integrity of the organ of Corti.

A small group claims, in general terms, that CM is not an indication of auditory function (208, 266, 321, 332).

Kobrak and his group (131, 261, 262) eliminated the middle ear reflexes by damaging the cochlea but produced little or no change of CM. Andreev, Arapova and Gersuni (14) and Perlman and Case (312) noticed that in man CM reaches a maximum while loudness still increases. Lempert et al (281) observed that primates, who apparently can hear very well, yield very low CM voltage.

H. Summating Potential

The summating potential (SP) which was discovered by Davis, Fernández and McAuliffe (113) is of principal concern in the experiments reported in Chapter IV. However, because the identification of this potential is so recent there is very little literature relating to it.

Three techniques paved the way for a clearer picture of the components of the electrical responses of the cochlea. The first involves placement of the electrodes exactly opposite in the same turn so that a straight line joining them is perpendicular to the basilar membrane. In this way CM at each electrode will be exactly 180° out of phase and AP exactly in phase. The second technique is to add the responses from the two electrodes (both referred to the neck) so that the out-of-phase CM components cancel out or else to subtract the responses from each electrode so that the in-phase AP components cancel out.

The third technique is to tailor a rectangular pulse so that a single frequency predominates. The acoustic signal then becomes a series of six or seven sinusoidal waves

with their envelope showing a gradual build-up to a maximum at about the center and then tapering off at about the same rate as the build-up (123). "Tone-pips" of 500, 2000, and 8000 cps basic frequency were used by Davis, Fernández and McAuliffe (113).

With AP canceled from the picture, the CM response to the 500 cps or the 2000 cps pip is a good reproduction of the pattern of the acoustic stimulus. The CM response to the 8000 cps pip also presents a faithful reproduction of the stimulus except that the baseline appears displaced. This displacement is obvious even in the presence of AP in the composite responses. The polarity of the displacement is negative (electrode referred to neck) in scala vestibuli and is positive in scala tympani.

The authors determined the following characteristics for the additional slow component, the component which is displacing the baseline, and which they call the "summating potential" (SP). SP is like AP in that its polarity does not change with a reversal of acoustic polarity. However, SP differs from AP in that its apparent source is in the organ of Corti and its polarity is opposite in scala vestibuli and scala tympani. SP is unlike CM in that SP outlasts the mechanical movement. In addition, SP continues to grow with intensity after CM has reached a maximum or is even decreasing. Davis and his colleagues claim that SP is more resistant than CM to injury to the cochlea and to anoxia.

Davis and his co-workers (113) conclude that (1) SP is an individual potential, distinct from CM and AP, and (2) SP is probably the excitatory process which the hair cells initiate in the nerve fibers connected to them.

I. Purpose of Present Investigation

The purpose of the present investigation is threefold: (1) to study the behavior of AP, CM and SP under identical conditions, (2) to analyze SP and to identify, if possible, the anatomical structures producing it, and (3) to examine critically previous interpretations of these electrical responses.

CHAPTER II

ANATOMY

Guinea pigs were used almost exclusively in this study. The author used 75 guinea pigs in his own experiments and he made observations incidental to other investigations on approximately 80 guinea pigs. The author also used one cat and eight pigeons in his own work and made observations on the responses from three hamsters during experiments on these animals by other investigators.

The anatomy of the guinea pig's ear has been described by many authors (60, 91, 146, 147, 148, 192, 198, 297). Only the details of the anatomy which will contribute to the understanding of the following chapters will be repeated here. The fine structures of the inner ear are of principal importance for this study and they will be treated in detail in a succeeding section. However, a brief picture of the middle ear of the guinea pig will be given first.

A. Middle Ear

The auditory ossicles, their supporting ligaments, and the tiny muscles which act on the ossicles (tensor tympani, stapedius) are all contained in an air-filled capsule called the bulla. A thin bone forms the walls of this cavity. It is lined on the inside by a thin but tenacious mucous membrane.

In many mammals, including man, a portion of the large basal coil of the cochlea is the only part of the inner ear which protudes into the middle ear cavity. In the guinea pig, however, the entire apical portion and more than half of the remainder of the cochlea lie in the space of the bulla. A large portion of each turn is clearly visible through a hole made in the ventro-lateral surface of the bulla (148, Figure 1). Only a thin bony capsule is interposed between the membranes and fluids of the inner ear and the air within the bulla.

B. Inner Ear

In the experiments described in Chapter IV the recording electrodes were placed in the basal turn about 3.5 mm from the round window. A cross-section of the cochlea at this point (Figure V-1) appears qualitatively the same as a cut through the cochlea at any place along its length, except, of course, at the extremes.

Scala media or the cochlear duct divides the perilymphatic space into a scala vestibuli and a scala tympani. Scala media is bounded above by Reissner's membrane which extends from the top of the limbus to the upper portion of the spiral ligament. The lower boundary of scala media is the basilar membrane and the osseous spiral lamina and spiral ligament to which the basilar membrane attaches. The third side of this approximately triangular duct is the spiral ligament and the overlying stria vascularis. The vascular bed ends at Reissner's membrane and does not extend

into scala vestibuli.

The portion of the spiral ligament which extends below the basilar membrane is given additional support by a crest of bone which extends inward from the bony capsule of the cochlea (148). The bony crest is present only in the basal turn.

The organ of Corti which rests on the basilar membrane is of primary interest because the sensory cells or hair cells are contained in the organ of Corti. The external hair cells (EHC) and the internal hair cells (IHC) are separated by the pillars or rods which form the tunnel of Corti. The groups of hair cells lie parallel to their respective tunnel rods and consequently the EHC and IHC are inclined at about 60° to each other in this portion of the cochlea (147).

The EHC are long and cylindrical and the IHC are more flasked-shape. The cellular contents of EHC and IHC appear similar. The morphology of the cells does not suggest that there might be a difference in function between the EHC and IHC.

The fibers of the auditory nerve have their origin on the hair cells and it is generally presumed that the mechanical activity in the cochlea is translated into nerve impulses by the intervening action of the hair cells. No function has been attributed to the other cells of the organ of Corti than that of mechanical support.

The exact form and composition of the tectorial membrane remains undetermined because of the difficulty of examining the membrane in the living animal. It is generally agreed (62, 212, 318, 319, 354, 373, 442), however, that the tectorial membrane is a non-living, gelatinous mass that occupies a large portion of scala media.

The tectorial membrane which lies over the organ of Corti is attached to the limbus. Whether the membrane attaches to the organ of Corti is not certain. However, it is almost certain that the tectorial membrane is at least functionally connected to the hair tufts of the hair cells (62, 319, 354, 373, 442).

The nerve fibers which originate in the organ of Corti have their cell bodies in the spiral ganglion. The nerve filaments course from the organ of Corti through the osseous spiral lamina to reach the spiral ganglion. The ganglion is encased in a thin bony shell which lies between the fluid-filled ducts of the cochlea and the center core of the cochlea, the modiolus. The central portions of the nerves enter the modiolus through small channels in the bone encasing the spiral ganglion and all the fibers leave the cochlea together through the internal auditory meatus.

CHAPTER III

PROCEDURES AND APPARATUS

A. Selection of Guinea Pigs

Only guinea pigs with apparently normal hearing were used in this study. The sole criterion for normal hearing was a positive Preyer's reflex, that is, the pinna showed a definite twitch when a sudden noise was made near the animal. Precautions were taken to assure that the guinea pig reacted to the sound and not to any visible movements or air currents which occurred during the production of the sound.

Most of the guinea pigs weighed between 250 and 350 grams. Only animals with dark fur were chosen. Coloration of the fur usually insures a strong pigmentation of the stria vascularis in the cochlea. The pigment shows through the thin bony capsule of the cochlea and provides a landmark for placement of the electrodes (see Section C).

B. Surgical Approach to Cochlea

The guinea pigs were anesthetized with Ciba's Dial with urethane (diallybarbituric acid with urethane and monoethylurea), 0.5 cc per kilogram of body weight. Injections were given intraperitoneally.

An incision was made in the skin from behind the pinna ventrally to just beyond the angle of the mandible. The mandible was exposed and the muscles were cleared from

angle. This tip was then cut away. After further dissection and retraction of the muscles in the area, the bulla was exposed.

The periosteum was cleared from the anterior aspect of the bulla and a hole was drilled in this section with a dental burr. The cochlea is clearly visible through such a hole. The hole was drilled large enough to permit a needle to enter almost any portion of the basal turn. If the apical portion was to be explored the hole in the bulla had to be extended anteriorly. An approach to the round window was best made by an accessory hole on the posterior aspect of the bulla.

C. Electrodes and Their Placement

The electrodes used in the experiments were No. 38 enamel-insulated silver wire. One tip of the wire was cut diagonally to give a smaller point and the insulation was scraped from about a half of a millimeter of the tip. The insulation was scraped from about 1 inch of the other end of the wire and this end was soldered to a metal lug to which a clip lead could be attached. At about 3 inches from the sharpened tip, the electrode was attached by wax to a metal rod. The rod was set in the carrier of a micromanipulator which guided the electrode to the cochlea.

To accommodate the sharpened tip of the electrodes, holes were drilled through the bony capsule of the cochlea. A three-sided steel needle held in a vise was used free hand (under binocular magnification of 7X) to drill the

holes. Drilling was stopped when fluid began oozing from the cochlea enough to wet the bone dust around the hole. The holes thus created were about 120 μ to 150 μ in diameter.

In the basal turn the bone is too thick usually for the stria vascularis to be visible. (In the more apical turns the stria is clearly visible as a dark band and serves as a landmark for scala media.) Therefore scala vestibuli, which must be entered above the stria vascularis, has to be located in another way. The hole was always drilled in the basal turn very near the angle between the large basal turn and the more recessed second turn.

The hole in scala tympani was always made just below a white line which courses around the middle of the basal coil. This white line marks the position of the crest of bone that is located at the extremity of the portion of the spiral ligament which is in scala tympani.

The two holes were so placed that the plane of the electrodes was exactly or nearly perpendicular to the basilar membrane. Such a placement insures optimum cancellation of in-phase or out-of-phase potentials (see Section D). The hole in scala tympani (It) was made in the most accessible portion of the bulging basal coil. This position is approximately 3.5 mm from the round window. If a line were to be drawn from this hole to the tip of the apex, the hole in scala vestibuli (Iv) would lie slightly medial to it, toward the umbo of the eardrum.

Enough pressure was exerted by the micromanipulator to seat the electrodes firmly in the holes drilled for them. Additional pressure was exerted to cause the electrodes to bend and to touch the drilled edge of the bulla. The wires were anchored to the bulla by dental cement and after the cement had dried the electrodes were removed from the rod which had been used as a supporting guide. The guinea pig was then free to move without danger of dislodging the electrodes from the holes.

After the electrodes were secured, the wound was closed with Michel clamps. The lug end of the electrodes extended through the closure and the electrodes were marked for identification.

D. Electroacoustic Apparatus

Davis et al (116) depict diagrammatically (their Figure 1) the stimulating and recording apparatus as it is set up in the animal laboratory of the Central Institute for the Deaf. The features of this system are explained in detail in recent papers by Davis and co-workers (113, 116, 123, 149). The portions of the system used by the present writer will be reviewed here.

1. Recording System.

The signals picked up by the recording electrodes (reference electrode clipped to muscles in the wound) are delivered to a pre-amplifier (three independent channels) with a balanced push-pull input. Each section of the pre-amplifier is connected to a cathode ray oscilloscope. The

three oscilloscopes are mounted side by side closely enough so that all three can be conveniently observed or photographed simultaneously. The sweeps may be controlled independently or all three can be controlled by the same circuit. The frequency response characteristic of the over-all recording system is essentially flat over the frequency range used in these experiments, about 100 to 10,000 cps. The sensitivity was always adjusted so that 100 mm peak-to-peak deflection on the oscilloscope represented 100 μV rms.

By a simple switching arrangement it is possible to add the output signals from two of the channels or to subtract them. In the case of addition (Iv + It) the components of the responses which are equal in magnitude but opposite in phase are eliminated. If the magnitudes are not the same the sensitivity of one channel can be altered until "cancellation" is perfect or optimum. Cochlear microphonics are completely eliminated by this arrangement when the electrodes are placed exactly opposite each other. When the channels are connected in opposite phase (Iv-It) the components which are normally in phase are subtracted from total signal. The action potential spike which is in phase and almost identical in amplitude at all electrodes in the basal turn is canceled by this arrangement.

During many of the experiments the changes in the responses were too rapid to be measured on the tube face. In these cases the response patterns were photographed for future examination. The 35 mm film was enlarged on a

microfilm reader so that the patterns appeared as large (or larger) as they originally were on the oscilloscope tube face. Measurements were made on the screen of the microfilm reader.

2. Generation of Accustic Stimuli.

Sinusoidal signals are generated by a General Radio beat-frequency oscillator (1304-A). Rectangular waves are created by a Grass square-wave stimulator (pulser) and throughout these experiments the waves were pulsed at 20/sec.

The rectangular waves can be fed directly to the loudspeaker which then produces an accoustic click or else the signals can first be sent through one or two sound-effects filters (UTC 4C). Usually the two filters were used in cascade and both the high and the low pass cut-off of each were set at the same frequency. Each filter has an attenuation of 18 db per octave and as a result the nominal frequency strongly dominates the signal delivered to the loudspeaker.

Before they reach the loudspeaker, all the signals are first sent through Daven attenuators with 20 db and 1 db steps, (total 110 db) allowing a distortion-free range of attenuation of 90 db. From the attenuators the signals go to a Langevin 101 output amplifier with a fixed gain. There are 30 db more of usable attenuation in 10 db steps to adjust the signal output (60 db in all). The effective

range of attenuation for both pads combined can be extended approximately 25 db without introducing excessive hum or distortion.

A switch on the control panel allows either the signal from the oscillator or from the pulser to pass through the attenuators and amplifier to the loudspeaker. Another switch changes the connections so the electrical polarities (and hence acoustic polarities) of the signals are reversed.

In all but one experiment (cf. Chapter IV, Part I) the loudspeaker was an Atlas PM-25 coupled to 5 feet of garden hose. In the earlier experiments (G-1 to G-24), the open end of the hosepipe was maintained about 3 cm from the guinea pig's ear. In the later experiments a metal speculum was sewed into the animal's ear and the broad end of the speculum was inserted into the open end of the hosepipe.

The frequency-response characteristic of the electroacoustic system shows a strong resonant peak near 2000 cps and a series of smaller peaks above and below that frequency. At 4000 cps the response of the system is very poor. The efficiency of the system increases above 4000 cps and there is a definite peak at 8000 cps. Beyond 8000 cps the response again becomes very poor.

When the sound-effects filters are set to pass frequencies only above 5000 cps, the characteristics of the speaker system further filter the signal so that 8000 cps becomes the dominant frequency. The original rectangular

wave is thus finally converted into a series of six or seven waves which build up to a maximum by the third or fourth wave and then decay at about the same rate at which they grew. Such a signal is called a "tone-pip."

When the filters are crossed at 2000 cps the strong resonance in the system accentuates that frequency and a 2000 cps pip results. There is a strong enough resonance near 500 cps to allow for a clear 500 cps pip. The system also permits the generation of tone-pips of 3000, 1000, 250, and 100 cps. Figure IV-1 (B, F, J) (cf. Chapter IV) shows the cochlear microphonic responses to these pips. The reproduction of the stimulus (except for the asymmetry with respect to the baseline) is as faithful as the reproduction by a microphone placed in the sound field.

In the following chapter the strengths of the acoustic stimuli are given in decibels above or below the level of stimulus necessary to produce a just-visible action potential response. However, in order to assess the absolute thresholds for some of the responses it was necessary to have a calibration of the electroacoustic system in terms of sound pressures. For this calibration the speculum was connected to a 1 cc brass coupler. This is approximately the volume of air beyond the speculum in the external auditory canal of the guinea pig. A calibrated condenser microphone (WE 640AA) was used to measure the rms sound pressures generated in the cavity in decibels above 0.0002 microbar, for given voltages impressed across

the terminals of the loudspeaker. These voltages were then related to the attenuator settings on the stimulus control panel. It was assumed that the sound pressure generated in the 1 cc coupler was the same as the pressure generated at the eardrum of the guinea pig. Obviously, the two situations are not identical. The external auditory meatus has not the rigid walls of the brass coupler. The acoustic impedance presented by the eardrum, ossicular chain, and middle ear cavity is not the same as the impedance of the microphone diaphragm and its mountings. Possible acoustic leakage in the canal of the guinea pig is difficult to measure or reproduce. However, this system of calibration was the most satisfactory one available.

CHAPTER IV

EXPERIMENTAL RESULTS

PART I. NORMAL PATTERNS

In these experiments very few observations of CM responses to pure tones differ from descriptions in previous literature even though in this study CM was viewed by itself in completely normal animals. Therefore, comments on pure tone responses will be restricted to several confirmatory observations.

A. Normal Patterns in Response to Tone-Pips 30-40 db above Action Potential Thresholds

1. Responses from the Basal Turn (Figure IV-1).

a) 8000 cps pip

The 8000 cps pip makes the best starting point because there is at least partial temporal separation of the components in response to it. In the response at the electrode in scala vestibuli of the first cochlear coil (Iv) the first potential to appear is CM (Figure IV-1-A). It reproduces the acoustic pip exactly. The polarity of the individual waves reverses with a reversal of acoustic polarity.

The main portion of the pip, and the CM which reproduces it, terminates before the beginning of the sharp negative spike, which represents the action potential. When the stimulus is 30 to 40 db above the threshold for AP, the

RESPONSES TO TONE-PIPS

30-40 DECIBELS ABOVE ACTION POTENTIAL THRESHOLD

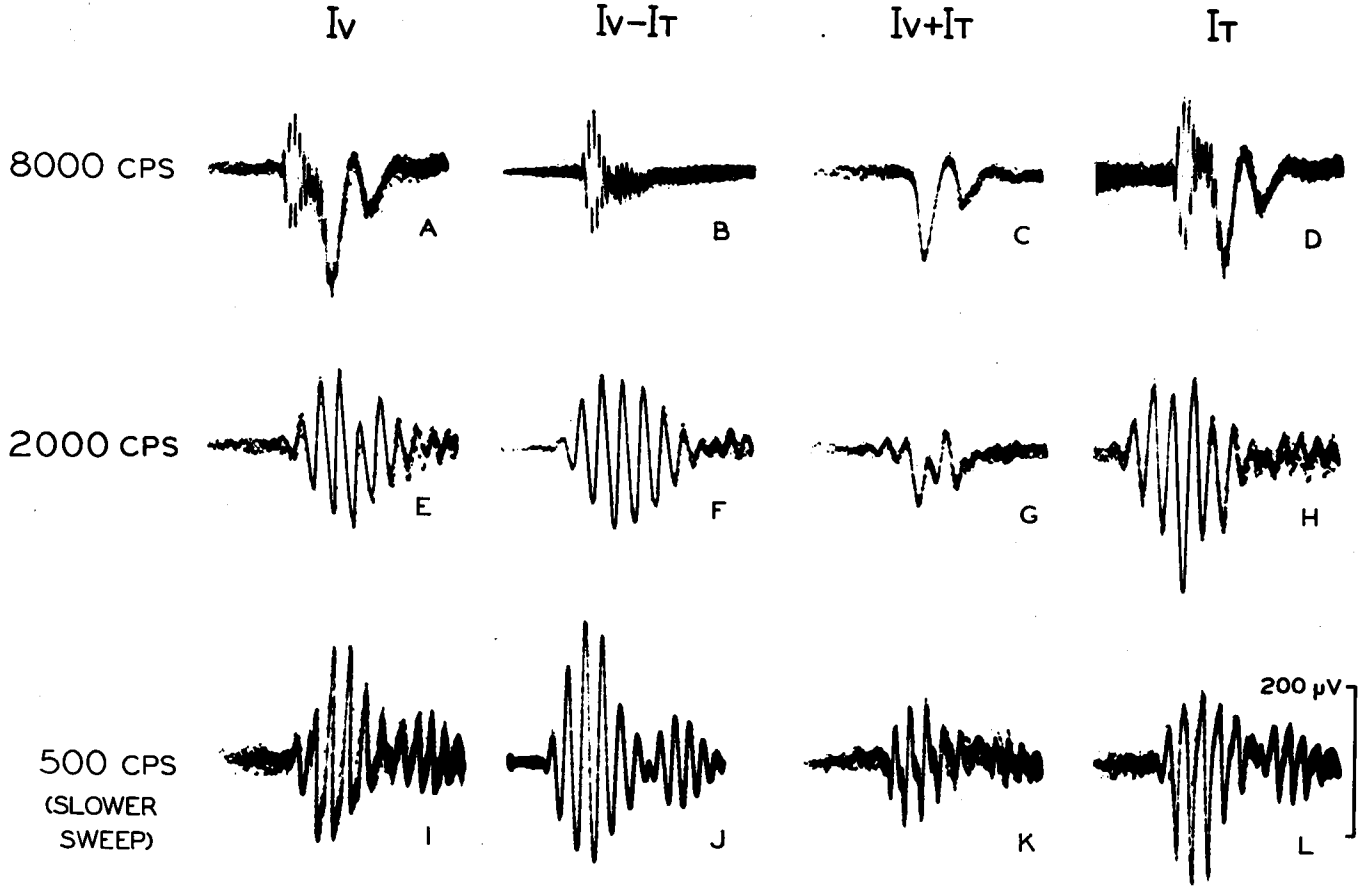


FIGURE IV-1

spike starts at about 1 msec after the beginning of the first CM wave. The AP spike reaches its peak in 0.3 msec after the foot of this spike appears. The potential drops to zero, i.e., returns to the baseline, in about 0.6 msec after the start of the initial drop or in about 0.3 msec after the peak of the AP spike. A small positive peak follows in about 0.3 msec after this return to the baseline or about 0.8 msec from the beginning of AP.

Further course of the primary AP, if there is any more of it, is obscured by the appearance of a second action potential spike from the secondary neurons in the cochlear nucleus. This is also a negative spike with about the same temporal course as the primary AP. A succeeding positive wave is present but the wave is too difficult to assess because it is so small.

As Davis et al (113) have shown, this AP pattern does not change with reversal of acoustic polarity and reversal does not alter its latency.

What Davis and his group call the "summating potential" (SP) manifests itself in Iv by the negative displacement of the baseline. Between 30 and 40 db above the AP threshold the displacement begins about 0.5 msec after the beginning of CM. SP grows in amplitude until it is interrupted and obscured by the large AP spike. SP remains negative with either acoustic polarity.

In scala tympani of the first turn (It)(Figure IV-1-D) everything in the temporal pattern of the action potential

response is the same as it is in Iv. CM is also the same except that each wave is of opposite polarity. The polarity of SP is also opposite; in It it is a positive displacement of the baseline. The amplitudes of all responses are of the same order of magnitude in both Iv and It.

Figure IV-1-B shows the responses of It subtracted from those of Iv. With AP gone SP can be seen prolonged beyond the beginning of AP. In the example illustrated (40 db above AP threshold) the apparent beginning of SP is at 0.5 msec after the beginning of the first CM wave. SP reaches a peak of 20 μV in approximately 0.5 msec (or 1.0 msec after the beginning of CM) and finally returns to the baseline in about 2.5 msec after the start of CM.

When the responses from It are added to those from Iv (Iv + It) CM is eliminated, if cancellation is perfect, and the baseline is flat signifying the elimination of SP as well (Figure IV-1-C). Time relations for the AP spike are as they were in the uncanceled patterns.

b) 2000 cps pip

In the response to the 2000 cps pip there is no temporal separation of components. There is the pattern of the stimulus with a large AP depressing one of the waves, the fourth positive peak in Iv. There is no indication in Iv of a summating potential, i.e., no general displacement of the baseline. In It the pattern is the same except for the 180° phase difference for the CM waves and for the exaggeration of the fourth negative peak of CM by AP

(Figure IV-1-E, H). In Iv-It CM reproduces the stimulus exactly (Figure IV-1-F).

For Iv + It CM cancels out but several AP spikes remain, separated by full wavelengths (Figure IV-1-G). One wave is always considerably larger than the others at the level shown in the picture, i.e., 30 to 40 db above the threshold for AP. There is no indication of a general displacement of the baseline.

c) 500 cps pip

The response pattern for the 500 cps pip is also a composite picture without temporal separation of the components. The distorted wave forms make it difficult to decide whether CM or AP dominates the responses. In Iv there is asymmetry of the total pattern (Figure IV-1-I). In most cases the displacement is clearly in a positive direction but sometimes it is indistinct. In It the picture is reversed but it is hard to say, just from looking at uncanceled patterns, whether the negative asymmetry is caused by a "summating potential" or by asymmetrical action potential waves (Figure IV-1-L).

Responses from Iv-It (CM) to the 500 cps pip duplicate the acoustic stimulus except that there is a fairly definite positive asymmetry (Figure IV-1-J). For Iv + It (Figure IV-1-K) the responses are all AP. AP has a large positive phase as well as a negative spike and these phases are not always equal in amplitude. At no intensity is the inequality of the two AP phases large enough to

account for much of the positive asymmetry in the uncanceled Iv response, or for the negative asymmetry in It.

d) 100, 250, 1000 and 3000 cps pips

Pips of 100 cps and 250 cps elicit response patterns like those resulting from the 500 cps pip but, naturally, with their own frequencies determining the CM frequencies. The guinea pig's ear is not very sensitive to these frequencies but even without distortion the responses show a positive asymmetry.

The 1000 cps pip often behaves like the 500 cps pip but many times it produces no asymmetry and is like the 2000 cps pip. Responses to the 3000 cps pip were exactly like the responses to the 2000 cps pip in about 15 animals in which the responses to the 3000 cps pip were examined.

e) 4000 cps pip

A frequency of 4000 cps is critical because here and for slightly lower frequencies there is a single AP spike, like the one produced by the 8000 cps pip. The Atlas PM-25 loudspeaker with its garden hose attachment is very inefficient at 4000 cps. To produce pips in this frequency range a PDR-10 earphone was employed as the sound source. It was fitted with an aluminum adapter which permitted the phone to be coupled to a thin plastic tube. The other end of the plastic tube was cemented into a metal speculum which could be sewed into the guinea pig's external auditory meatus. The electrical square wave pulse was sent through the two sets of sound-effects filters which were crossed

nominally at 4000 cps. The basic frequency of the electrical responses to this pip was 3500 cps. This frequency was increased by decreasing the length of the plastic tube. When the tube was cut to its shortest usable length, the basic frequency of the pip was about 4100 cps.

When the basic frequency of the pip is about 3500 cps asymmetry of the CM responses is uncertain in both Iv and It. At 3950 cps it is still not clear but there is an indication of a slight negativity in Iv. With a pip whose basic frequency is 4100 cps the negativity in Iv is clear though small. There is a very slight indication of positive asymmetry in It. Although SP is not pronounced at these frequencies the <u>difference</u> between Iv and It becomes quite evident.

2. Responses from other Positions in the Cochlea.

Responses from the round window (referred to the neck) are like those from It but SP is not so pronounced. There is no evident asymmetry of the 2000 cps pip except that caused by AP. There is a pronounced negative asymmetry of the responses to the 500 cps pip, more than can be expected to be due only to AP.

The apical electrode was always placed in scala vestibuli and referred to the neck. With an unfiltered click whose original wave is a rarefaction (negative acoustic polarity) the initial CM wave is negative. For the 8000 cps pip, SP is as large at the apex as it is in

Iv but CM is smaller than in Iv. The 2000 cps pip appears as it does in Iv but AP seems much stronger. The very strong AP with the 500 cps pip obscures any possible positive asymmetry.

In general, electrodes placed in scala vestibuli and scala tympani of other turns and referred to the neck detect patterns like those from Iv and It respectively. At the time that these experiments were performed there was no technique for differential recording, i.e., scala vestibuli ± scala tympani, from any except the basal turn.

B. Thresholds

1. Pure Tones.

Data from 18 animals whose responses were judged normal were utilized along with the pure tone calibration of the acoustic system (Chapter III, pages 71 and 72) to obtain some thresholds for the guinea pig for pure tones in terms of sound pressure level. A response of nearly 3 μV peak-to-peak was about the smallest amplitude distinguishable from the noise of the baseline. The average of this threshold for the Iv-It combination are shown in Table IV-1.

Table IV-1

CM THRESHOLDS (3 μV) FOR PURE TONES

pure tone frequency	threshold in decibels*	S.D. in decibels	range in decibels*
8000	22	10.4	8 to 40
2000	38	6.6	24 to 49
500	47	9.1	32 to 62

*re 0.0002 microbar

The difference of 16 db between the 8000 cps and 2000 cps thresholds is significant at the 0.01 level of confidence. The difference of 9 db between the 500 and 2000 cps thresholds is significant at the 0.02 level.

2. Tone-Pips.

Thresholds for AP can only be judged with certainty (for most frequencies) from responses to tone-pips. Therefore, a calibration was needed for the pips in order to assign absolute values to the AP thresholds. A comparison was made between the dial settings necessary for the apparatus to produce a pip with the largest wave of its CM response having the same peak-to-peak magnitude as a pure tone response of the same frequency. The threshold response of 3 μV was chosen for the comparative measurements. These measurements were made on the same 18 animals used in the determination of the pure tone thresholds. It was assumed that the peak-to-peak pressure produced by the largest wave of the pip was the same as that produced by the steady-state pure tone. A relationship for the pips was thus established between the dial settings and the sound pressure levels. Justification for this assumption lies in the very small differences in the absolute thresholds determined for CM for both pure tones and pips (see previous and following table).

Table IV-2

CM AND AP THRESHOLDS (3 μV) FOR PIPS

pure tone frequency	threshold in decibels*		S.D. in decibels		range in decibels*	
	CM	AP	CM	AP	CM	AP
8000	21	7	10.4	8.4	-2 to 34	-8 to 24
2000	41	43	9.5	12.1	20 to 62	23 to 70
500	45	53	12.9	14.0	23 to 64	27 to 77

*re 0.0002 microbar

The difference of 20 db between the CM thresholds for the 8000 cps and the 2000 cps pips is significant below the 0.01 level of confidence but the difference of 4 db between the 2000 cps and 500 cps thresholds is only significant at the 0.30 level. For the two latter frequencies, the difference of 10 db in their action potential thresholds is significant between the 0.02 and 0.05 levels of confidence. The difference of 36 db between the AP thresholds for the 8000 cps and the 2000 cps pips is significant well below the 0.01 level.

For the same pip frequency the differences between the CM and AP thresholds are also appreciable. The 14 db greater sensitivity of AP for the 8000 cps pip is significant at the 0.01 level and the 10 db greater sensitivity of CM in response to the 500 cps pip is significant at the 0.10 level of confidence but the 2 db difference between AP and CM thresholds for the 2000 cps pip has no statistical significance.

Thresholds for SP are less easily measured because it is more difficult to detect a 3 μV displacement of a long segment of the baseline than it is to notice the same change in the restricted portion of it displaced by a CM wave or AP spike. Under normal conditions there is no SP in response to the 2000 cps pip. SP in response to the 8000 cps pip makes its appearance at about the threshold for CM. For the 500 cps pip, SP is not definitely evident until CM has reached an amplitude of at least 20 μV.

Throughout the remainder of the chapter comparative instead of absolute thresholds will be used. The zero value will be the action potential thresholds, and a stimulus will be defined as so many db APL (action potential level), i.e., decibels above the action potential threshold for that same pip.

C. Intensity Functions

1. Pure Tones.

Pure CM responses to pure tones, i.e., viewed from Iv-It, grow linearly with intensity. The slope of the curve of the logarithm of voltage output versus the logarithm of stimulus pressure is practically 1.0. No systematic trend toward a larger slope for lower frequencies was found (cf. Chapter I, page 14).

No investigation was made at high enough intensities to determine when the growth of CM ceased to be

a linear function of the stimulus. These measurements were purposely omitted in order to avoid any over-stimulation before the responses to the pips were studied. The few ears exposed to sounds of greater intensity showed some tendency to depart from a linear relationship at smaller response levels for high frequencies than for low frequencies.

2. Tone-Pips

a) CM

The growth of CM with pips of increasing strength was more closely observed (Figure IV-2). The slope of the intensity function is about 0.9, definitely smaller than unity, for the 8000 cps and 2000 cps pips but it is 1.0 for the 500 cps pip.

The curves in Figure IV-2 depart from a straight-line relationship at high intensity levels. Considering a 1 db difference from the extrapolated straight line as the limit of constant slope, this limit comes at 525 μV or less of the 8000 cps pip. For the 2000 cps pip the limit is 600 μV or more. The limit of the linear growth of CM with the 500 cps pip was measured in only two animals and in these cases the limits were 525 μV and 850 μV. (To avoid even temporary depression of responses the sound intensity was always kept below the level which would produce maximum CM voltage.)

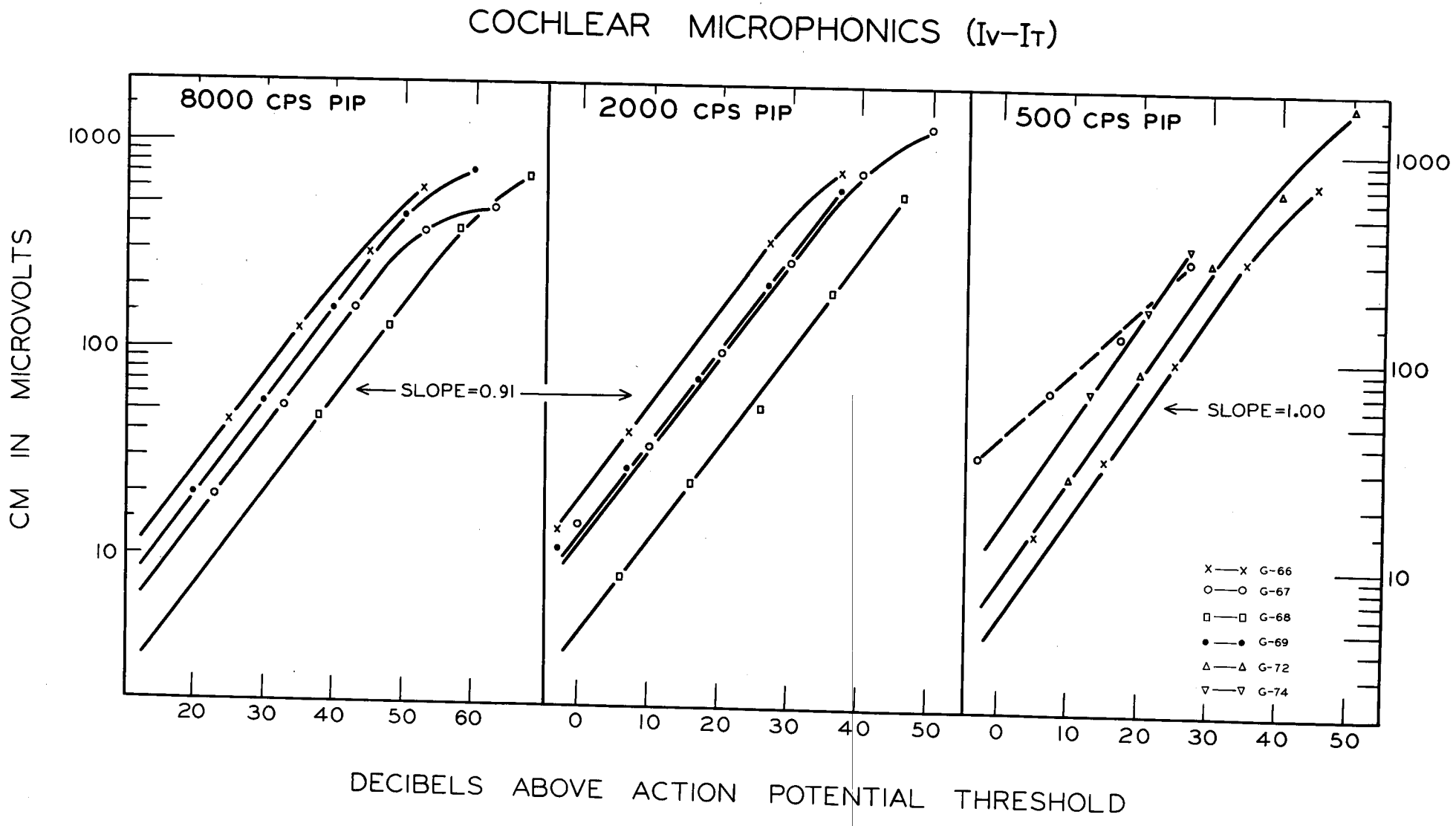

COCHLEAR MICROPHONICS (Iv–IT)
8000 CPS PIP
2000 CPS PIP
500 CPS PIP
1000
100
10
CM IN MICROVOLTS
SLOPE=0.91
SLOPE=1.00
20 30 40 50 60
0 10 20 30 40 50
0 10 20 30 40 50
G-66
G-67
G-68
G-69
G-72
G-74
DECIBELS ABOVE ACTION POTENTIAL THRESHOLD

FIGURE IV-2

b) AP

The growth of AP with intensity is not linear nor is it an exact power function for any of the pips used in this study. Its growth, as a function of the logarithm of the stimulus strength, is not linear over the entire range of pressures used but considerable portions of the growth curves are best described as linear.

Comparison between pips is difficult. The response to the 8000 cps pip has only one primary AP group but each wave of the 2000 cps and the 500 cps pips may have an action potential spike. Measurements can be made on the spike which is the first to appear at low intensities but with greater intensities a larger AP appears at least a wavelength earlier because most of the neurons then discharge earlier (113). An alternative is to measure the early wave only, ignoring the later AP at lower intensities, but this is necessarily not a complete picture of the growth of AP. The amplitude of each wave could be added and the total be plotted against the stimulus strength. Still another procedure (which also does not give a true picture) is to measure the size of the <u>largest</u> AP wave only. None of these measures are strictly comparable to the measurements made on AP produced by the 8000 cps pip.

AP in response to the 500 cps pip adds another complication because it has a positive phase which is approximately the same amplitude as the negative phase.

In this study, AP in response to the 8000 cps pip

was measured from the baseline to the tip of the negative spike. For the 2000 cps and 500 cps pips the same measure was made, but always on the largest wave.

The amplitudes of AP (by the criteria just mentioned) versus stimulus pressures in db APL are plotted in Figure IV-3. The curves are not linear although portions of many of them are nearly so, especially at the lower intensities. With the logarithm of AP voltage as the ordinate none of the curves follows a straight line but all of the curves of each group conform approximately to the same slope, a slope that suggests a power function much less than unity (Figure IV-4). This slope obtains only beyond 10 db APL. The rise from threshold to 10 db APL (decibels above the action potential threshold) is much more rapid. No responses were measured beyond 60 db APL for the 8000 cps and 2000 cps pips or beyond 50 db APL for the 500 cps pip because visible distortion of the individual waves often occurs just above these levels and, also, new families of AP appear.

c) SP

The summating potential in response to the 8000 cps pip, like the action potential, exhibits no linear growth as a function of the logarithm of the stimulus (Figure IV-5, lowest curves), nor does the logarithm of SP (absolute values) show a linear growth with logarithmic increases in sound pressure (Figure IV-6). None of the curves shown in Figure IV-6 conform to an exact power function and the

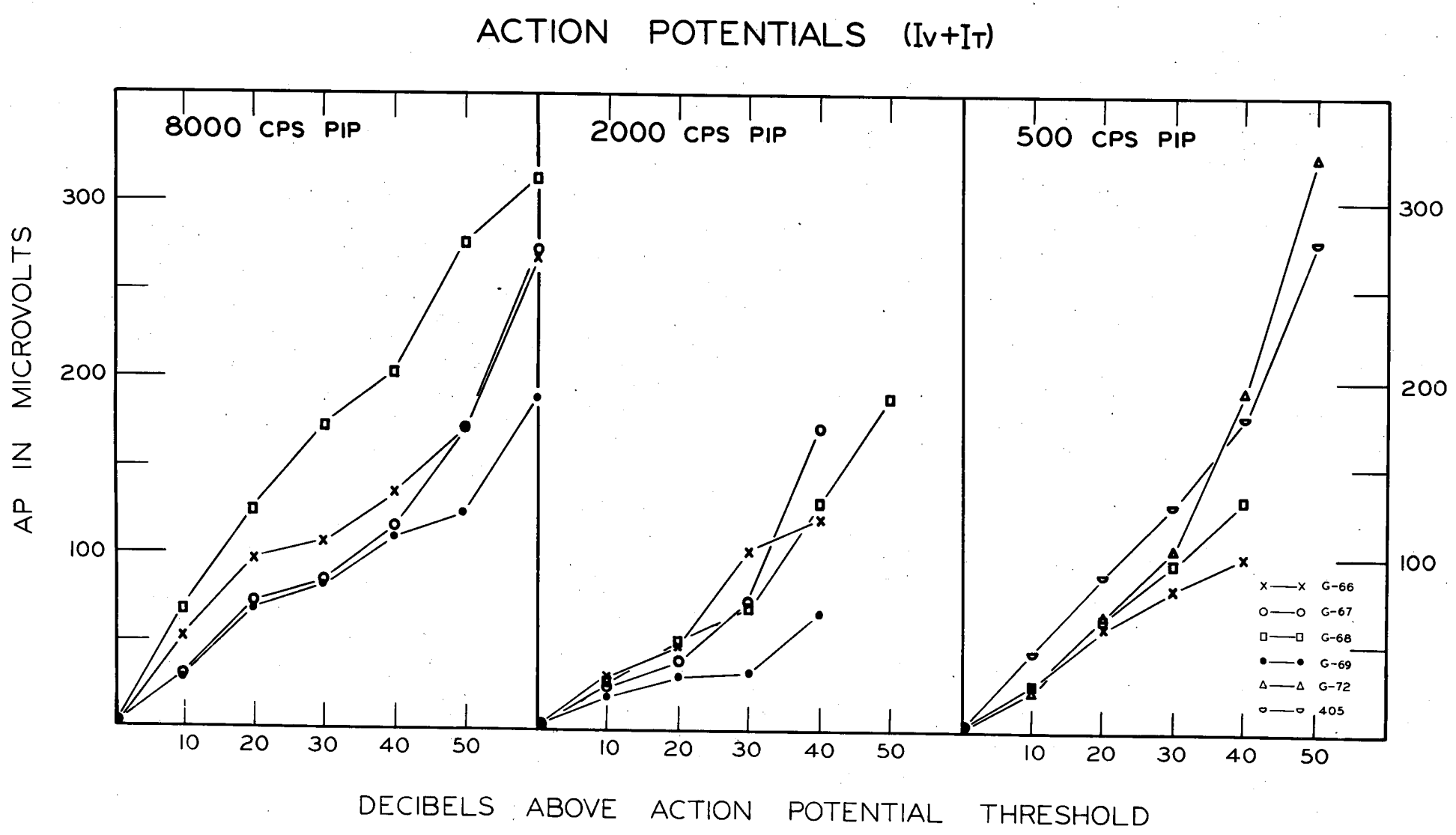

ACTION POTENTIALS (Iv+IT)
8000 CPS PIP
2000 CPS PIP
500 CPS PIP
AP IN MICROVOLTS
300
200
100
10
20
30
40
50
DECIBELS ABOVE ACTION POTENTIAL THRESHOLD
G-66
G-67
G-68
G-69
G-72
405

FIGURE IV-3

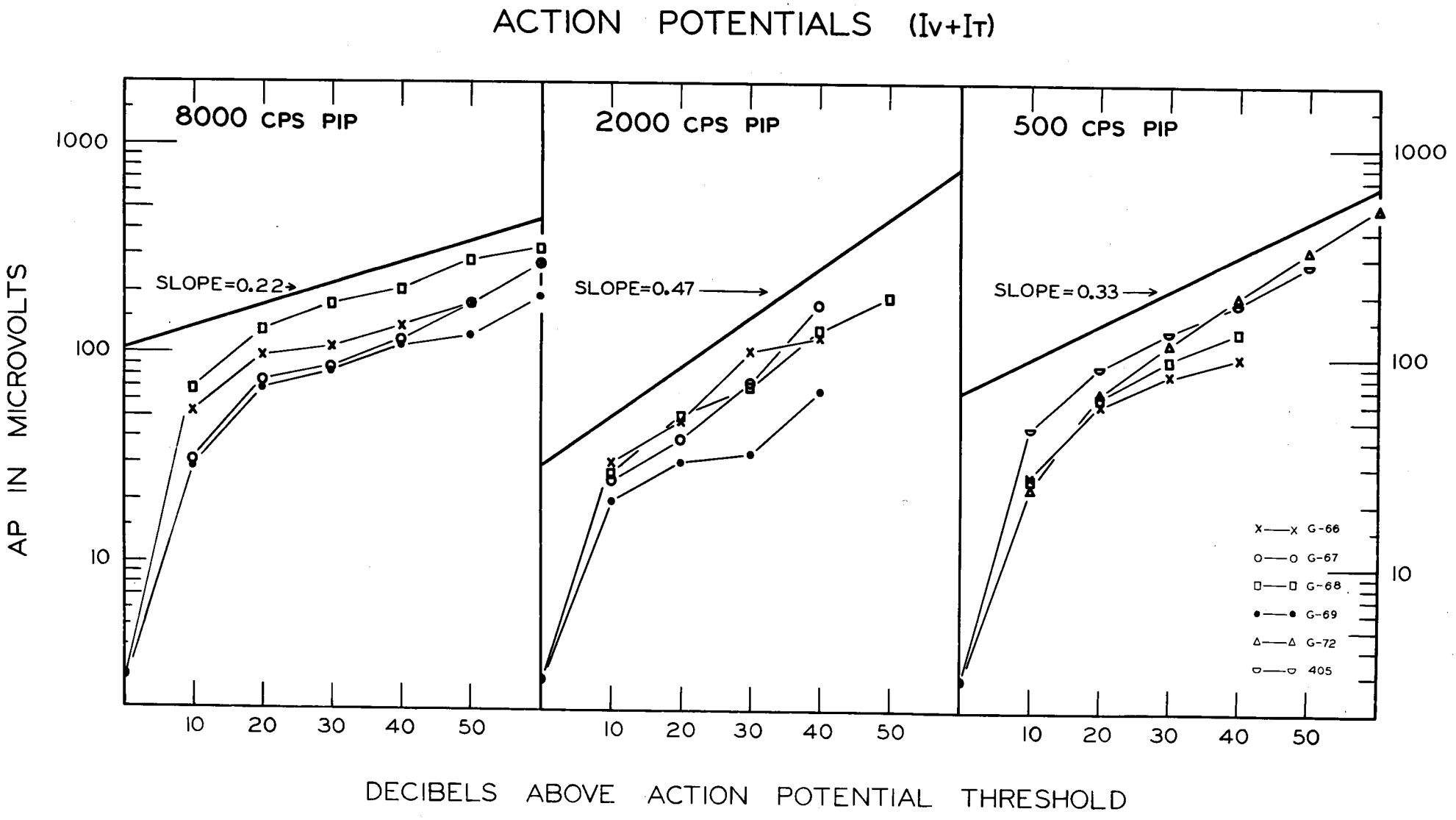

ACTION POTENTIALS (Iv+IT)
8000 CPS PIP
2000 CPS PIP
500 CPS PIP
SLOPE=0.22
SLOPE=0.47
SLOPE=0.33
AP IN MICROVOLTS
1000
100
10
10 20 30 40 50
DECIBELS ABOVE ACTION POTENTIAL THRESHOLD
X—X G-66
O—O G-67
□—□ G-68
●—● G-69
△—△ G-72
▽—▽ 405

FIGURE IV-4

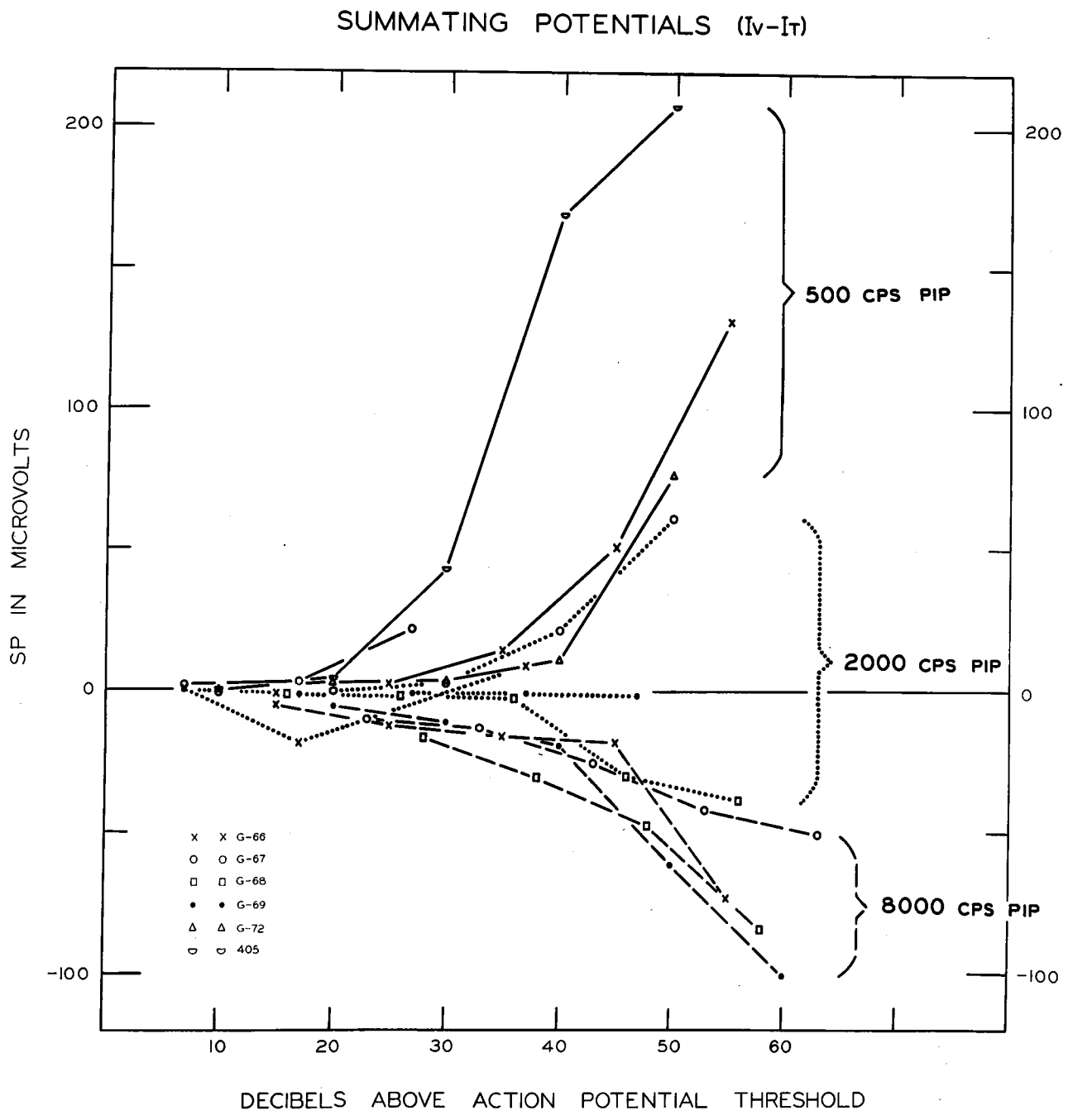

SUMMATING POTENTIALS (Iv-It)
200
100
0
-100
SP IN MICROVOLTS
500 CPS PIP
2000 CPS PIP
8000 CPS PIP
G-66
G-67
G-68
G-69
G-72
405
10
20
30
40
50
60
DECIBELS ABOVE ACTION POTENTIAL THRESHOLD

FIGURE IV-5

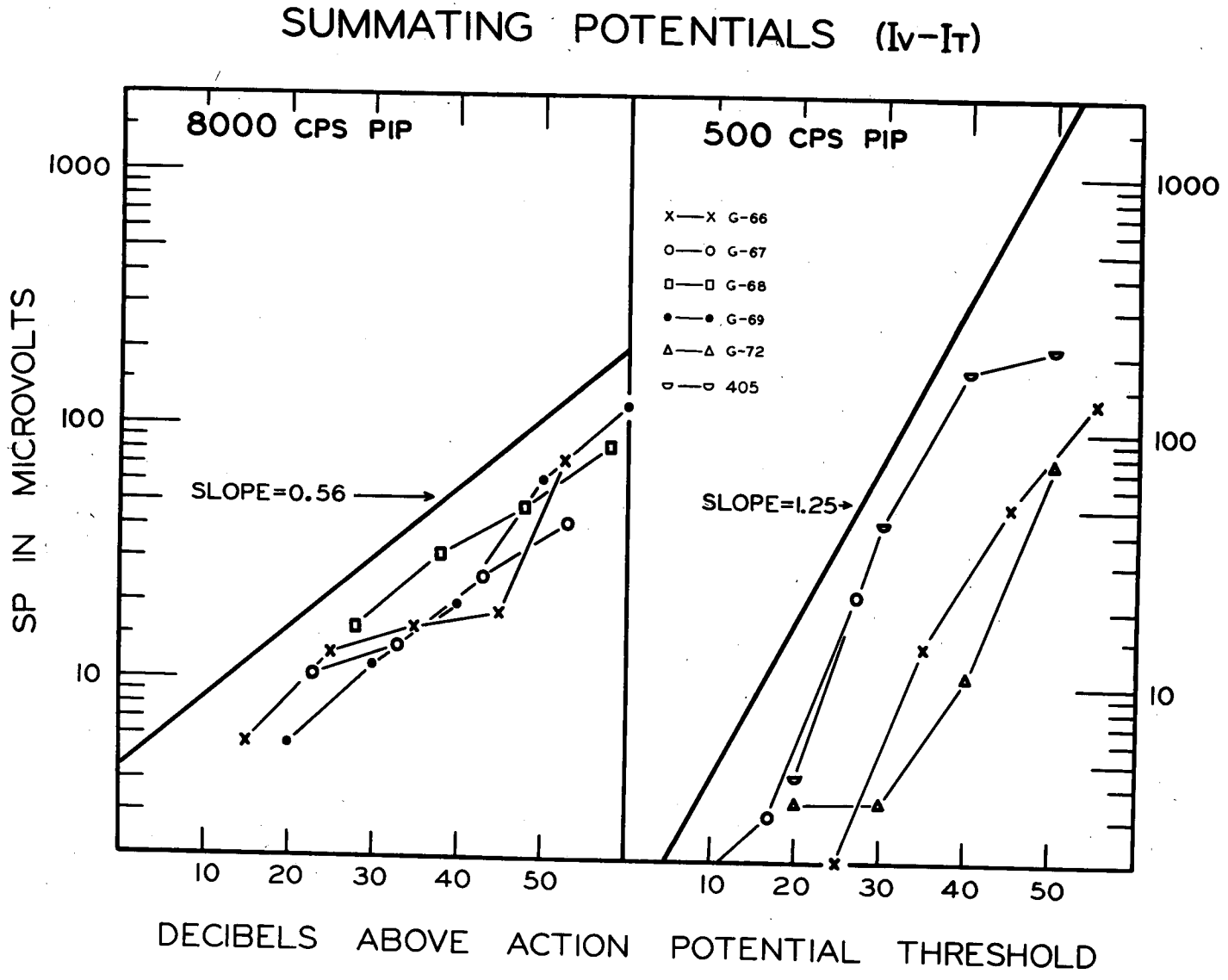

SUMMATING POTENTIALS (Iv-It)
8000 CPS PIP
500 CPS PIP
1000
100
10
SP IN MICROVOLTS
SLOPE=0.56
SLOPE=1.25
X—X G-66
O—O G-67
□—□ G-68
●—● G-69
Δ—Δ G-72
▽—▽ 405
10 20 30 40 50
10 20 30 40 50
DECIBELS ABOVE ACTION POTENTIAL THRESHOLD

FIGURE IV-6

irregularities are inconsistent from one guinea pig to another. However, the general trend of all the curves is definite. They follow a slope of about 0.6. The average amplitude at 50 db APL is about 50 μV. The largest value measured was 175 μV at 62 db APL. Up to 60 db APL there is no indication of bending or of flattening of the curves.

In order to determine SP or the displacement of the baseline for the 2000 cps pip, measurements were made on the CM responses from Iv-It. The amplitudes of the positive and negative peaks (starting from the zero potential baseline) of the largest CM wave were measured. If one of the peaks did not correspond to the maximum of the envelope of the pip, the measurement was made to the extrapolated maximum of the envelope. Up to 30 db APL there are no significant differences between the positive and negative phases of CM (Figure IV-5). The measurements at higher intensities often indicate appreciable asymmetry but there is no consistency from animal to animal in the polarity of this asymmetry. Difficulty in extrapolating to the maximum of the envelope probably introduces much of this difference and slightly imperfect cancellation of AP can also account for some of the deviations from symmetry.

Similar measurements were made on the CM responses from Iv-It to the 500 cps pip. There is a rapid increase in the positive asymmetry above 25 db APL (Figure IV-5). The highest single measure of the difference between the positive and negative phases was 260 μV at 55 db APL, which means a

displacement of the baseline by about 130 μV. The individual curves of the logarithm of SP versus changes in sound pressure in decibels do not indicate exact power functions (Figure IV-6) but like similar curves of SP for the 8000 cps pip they all tend toward a common slope, about 1.3 for this frequency.

d) Relations between CM, AP and SP

There is no constancy for any of the pips of the ratios: SP/AP, SP/CM, or AP/CM. The variations within each ratio are great, often by factors of 2 or 3. However, the variations show the same trend from animal to animal. This is another indication of the comparative uniformity of the curves of the same measure for different animals (Figure IV-2, 3, 4, 5 and 6).

D. Temporal Patterns

1. AP.

The action potential spike produced by the 8000 cps pip is delineated clearly enough from the other components of the response so that time measurements to its beginning and to its peak can be made with considerable accuracy. At 60 db APL the interval between the beginning of the first CM wave to the foot of the AP spike is about 0.8 msec. Responses from the few ears which could be driven beyond 60 db APL indicate that this latency is not reduced much with further increases in the sound pressure. With reduction in the intensity of the pip the latency of the beginning of the AP spike increases. Near threshold it is

at least 1.3 msec. At all sound pressure levels up to 60 db APL the peak of the AP spike follows the foot by about 0.3 msec. Most of latency can be attributed to the time of conduction of the nerve impulse along the peripheral branches of the auditory nerve to main trunk in the modiolus from which the AP spike apparently originates.

The lack of temporal separation of CM and AP in the responses to the 2000 cps and 500 cps pips makes latency measurements difficult for these frequencies. In addition the time relations of the AP responses from the secondary neurons are such that they overlap with the primary AP of the succeeding waves. Therefore, no latency measurements were made on the AP responses to these pips.

2. SP.

It is possible that there is no latency of SP with respect to CM. However, the interval from the beginning of CM to the measurable displacement of the baseline (indicating SP) increases from about 0.2 msec at 60-70 db APL to about 1.0 msec at 20-25 db APL.

Measurements from the beginning of CM to the peak of SP range from as much as 1.6 msec at 20 db APL to slightly less than 0.4 msec at 60 db APL. A glance at the response patterns to the 8000 cps pip shows that the peak of SP falls close to the foot of the AP spike. Measurements indicate that they do not coincide. At low intensities the foot of AP comes first but as the intensity increases the peak of SP appears as much as 0.5 msec before the beginning

of AP.

The course of SP or the displacement of the baseline for the 500 cps pip seems to follow the envelope of the pip.

E. Miscellaneous Observations

1. Deep Electrode.

In an experiment by Tasaki and Kahana (unpublished observations) an electrode was placed deep in scala tympani of the first turn against the bone of the modiolus. The silver wire electrode was cut at right angles to its length and tip was not sharpened nor stripped of its insulation. Therefore, with just the cut tip active, only potential changes in a restricted region near it were registered. This same experiment was repeated by the writer with Tasaki and the previous observations were confirmed. The only change noticeable in the pattern of responses to the 8000 cps pip was the greatly increased SP. At about 50 db APL SP was nearly as large as CM and nearly as large as the AP spike recorded from Iv + It. SP was 180 μV whereas with the more superficial electrodes it is only about 50 μV at 50 db APL. However, CM response to the 2000 cps pip (Iv-It) remained symmetrical about the baseline and the 500 cps pip produced CM which was displaced slightly positive in the records from Iv-It, just as with the superficial electrodes.

2. Masking.

Noise presented to the guinea pig's ear simultaneously

with an 8000 cps pip greatly reduces the AP response to the pip while it leaves CM unchanged in amplitude. SP is also reduced but not so much as AP.

In one experiment when the electrode in scala tympani of the basal turn was inserted as far as the modiolus (see above) the effects of noise from an air jet on the responses to an 8000 cps pip set at 50 db APL were examined. The microphonic activity produced by the noise was about 160 μV while CM produced by the pip was 235 μV, a difference of 3.6 db. CM from the pip was not measurably reduced by the noise. AP, however, decreased 9.0 db from 225 μV to 81 μV. SP decreased from 176 μV to 106 μV or about 4.4 db. Approximately the same relative changes in the presence of the noise occurred in the responses to the 8000 cps pip when the electrodes were in the normal, just penetrating positions.

3. Fatigue.

No special study of fatigue was made but there is no indication that the amplitudes of SP or AP are altered during prolonged stimulation by pips which are not intense enough to produce damage. The pips were always presented at the rate of 20/sec. The effect of varying the pulsing rate was not examined.

Likewise, no measurements were made to discover whether or not there is equilibration of AP responses to the pips, i.e., a rapid decrease in amplitude of AP to a

uniform level within the first few seconds of stimulation.

F. Responses from other Animals

Responses to pips were observed in a cat from an electrode on the RW. Responses from hamsters were also observed during experiments by Kahana and Fernández. In these experiments electrodes were placed on the RW and in It and Iv. Qualitatively, the responses from these animals were the same as those observed in the guinea pig.

Potentials from the pigeon were also examined. This animal has a more primitive cochlea and the responses from it differ appreciably from those of the guinea pig, cat and hamster. Cochlear potentials from the pigeon will be discussed in more detail in the following section.

PART II. CHANGES IN ELECTRICAL RESPONSES DURING DEATH AND ANOXIA

A. Post-Mortem Changes following Failure of Respiration

1. 8000 cps.

The normal responses to the 8000 cps pip have been described in Part I. Responses from Iv consist of the cochlear microphonics which reproduce the pattern of the acoustic signal, the action potentials, represented by a large negative spike followed by a smaller positive wave, and the summating potential which displaces the baseline negatively. At levels exceeding 40 db APL, CM waves appear beyond the main pip because the generating system also produces a smaller pip after the main one. CM produced by the secondary pip is superimposed on AP. However, the AP spike is much larger than those CM waves and AP dominates that portion of the oscillographic record of the cochlear potentials. During the experiments described in this section the intensity of the acoustic signal was always maintained at a constant level. Therefore, so that the greatly reduced responses could be viewed many minutes after death, the starting level had to be high and at these high levels the secondary pip was always present.

An 8000 cps pure tone was presented to the normal animal and a graph was constructed of the logarithm of the CM responses in microvolts against increases in sound pressure in decibels. From the resulting curve a level was chosen

which elicited CM responses near the upper limit of the straight-line portion of the curve. The intensity of the pip was adjusted so that the peak-to-peak amplitude of the largest CM wave was equal to the peak-to-peak amplitude of the pure tone response.

A switch on the stimulus control panel allowed simple changing from one signal to the other. While the animal was dying the signals were alternated so that the pip and the pure tone were presented to the animal at regular intervals. The responses to these signals were photographed and measurements were made from the film.

In all of these experiments the animals were killed by an overdose of Dial with urethane, usually 2 cc, given intraperitoneally. Several minutes after the injection of the anesthetic the guinea pig's respiration rate became slower and finally all breathing stopped. The heartbeat continued at a reduced rate for at least a minute after respiration ceased.

The changes in the responses to pure tones are the same as those described by Wever, Bray and Lawrence (423). CM decreases sharply, shortly after respiration ceases. This drop in CM becomes more gradual and the potentials reach a minimum. A "rebound" or increase in responses follows. Finally the responses shrink to a level lower than they were previous to the rebound and then disappear completely.

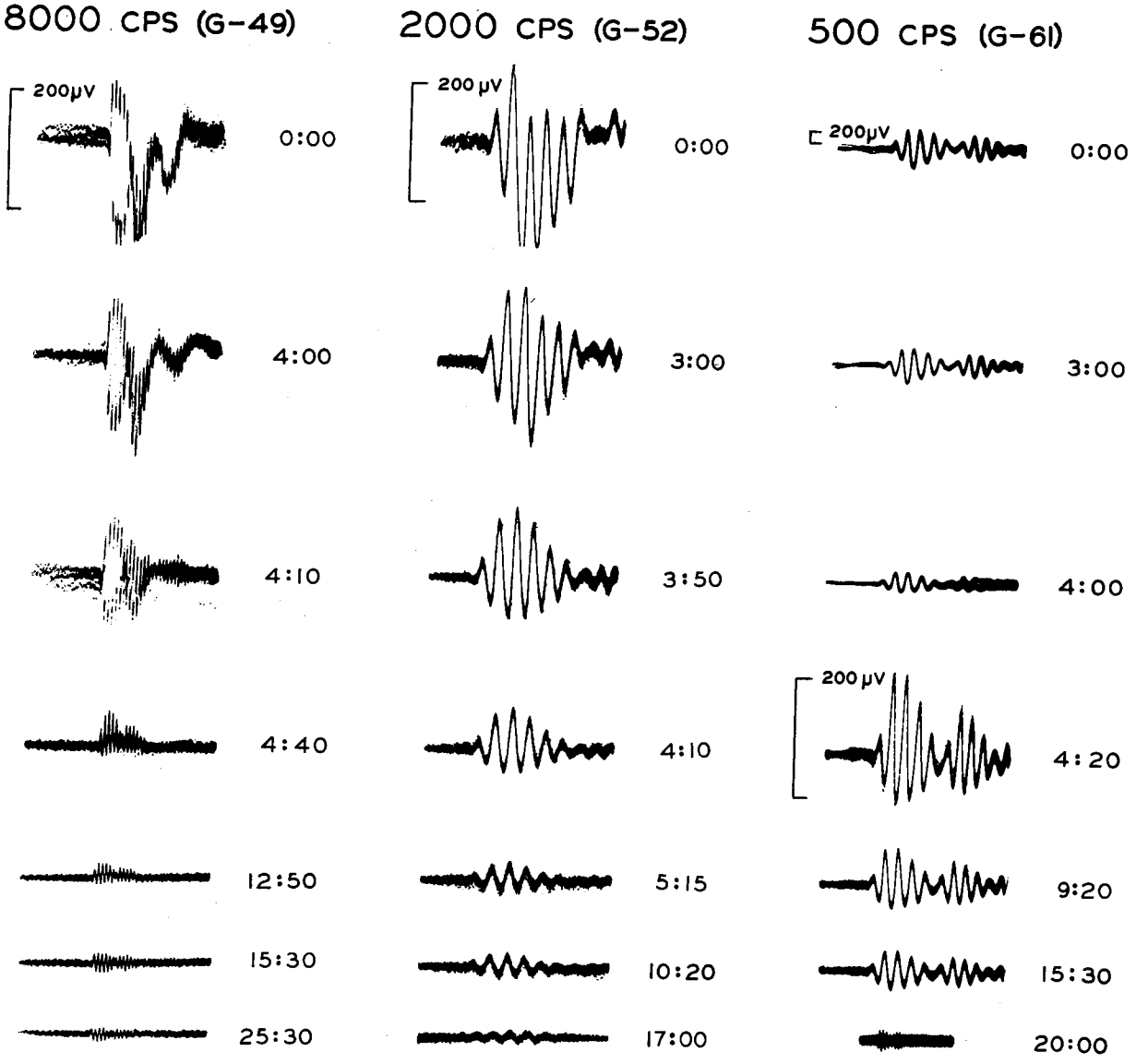
SP (as recorded from Iv) becomes positive during the initial drop in CM but after CM has passed its rebound SP again becomes negative in Iv and remains that way until all responses disappear. SP recorded from It becomes negative (while SP in Iv becomes positive) and it finally reverses to a positive polarity. In the responses to the 8000 cps pip AP disappears during the early rapid decrease in CM. Figure IV-7 illustrates these changes and Figure IV-8 depicts them graphically. The logarithm of the CM voltage was plotted in order to emphasize the rebound.

In addition to the four animals represented in Figure IV-7 and IV-8 there were two others in each of the 2000 cps and 8000 cps series. The changes of responses during death in these other animals exhibited similar time relations, and changes in amplitude were of the same order of magnitude as those depicted in the figures. Changes in CM shown in the figures and the measurements of the same changes in the other animals are very similar to those illustrated in the paper by Wever, Bray and Lawrence (423).

a) tone-pip

While CM is decreasing, AP also shrinks and the negative SP (from Iv) disappears. The last indication of AP vanishes just as SP disappears. A positive SP reappears immediately thereafter. In one animal (G-26), SP did not reverse although it became much less negative. This animal had been given 4 cc of Dial with urethane as a lethal overdose.

RESPONSES TO TONE-PIPS (Iv) DURING DEATH



TIMES TO RIGHT OF OSCILLOGRAMS ARE IN MINUTES AND SECONDS AFTER INJECTION WITH OVERDOSE OF ANESTHETIC

SLOWER SWEEP FOR 500 CPS PIP. SPEED OF SWEEP FURTHER REDUCED FOR LAST OSCILLOGRAM.

FIGURE IV-7

COCHLEAR MICROPHONICS—SUMMATING POTENTIALS DURING DEATH

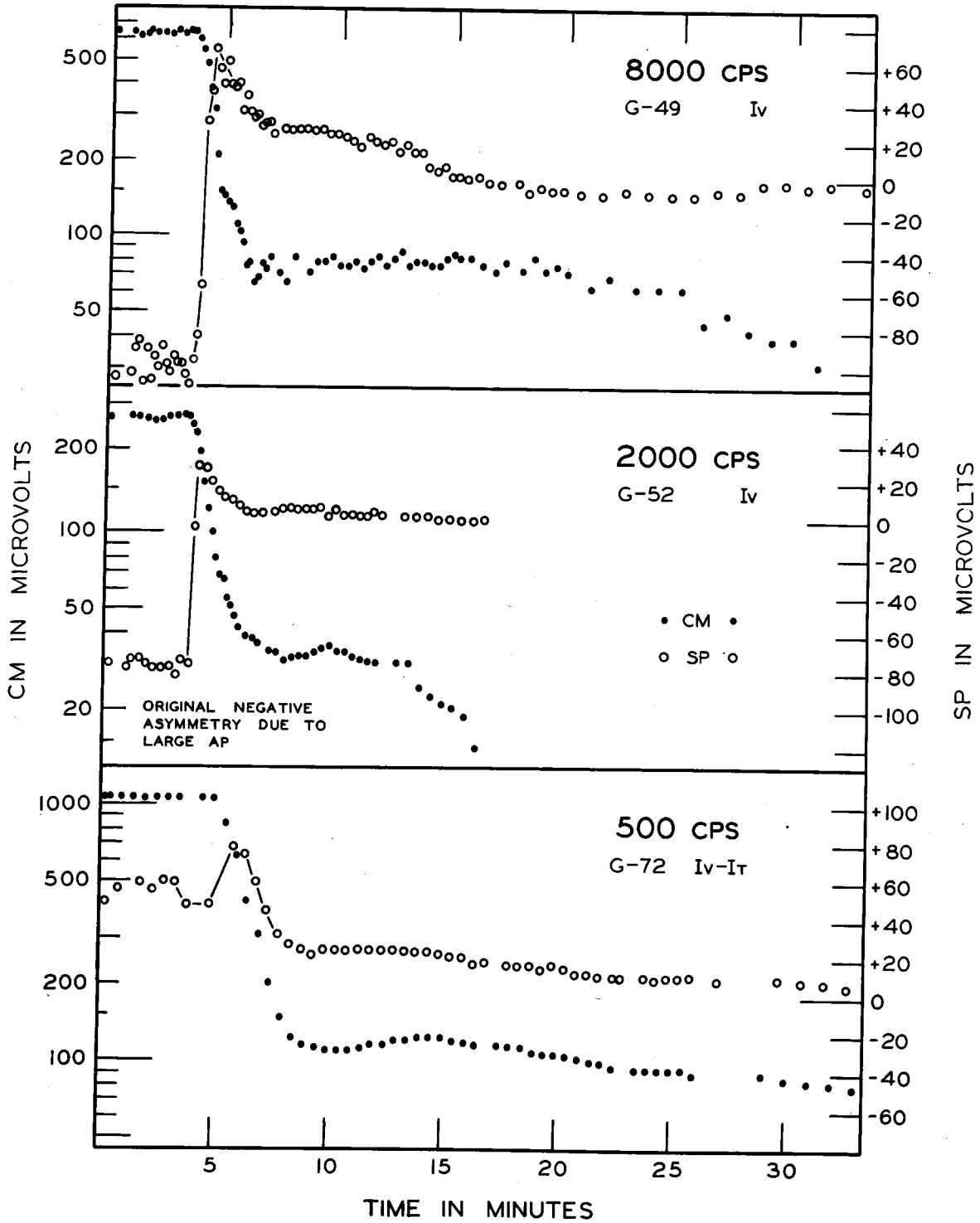


FIGURE IV-8

The positive state of SP is also transient and SP disappears in 5 min or more. A negative SP then appears and it remains as long as any measurable responses persist. The positive SP disappeared by 7 min (G-47) and 12 min (G-49) after the beginning of the decrease in CM. The final negative SP was observed for more than 3 hours after the death of some guinea pigs.

b) pure tone

After respiration ceases the CM response to the 8000 cps pure tone decreases rapidly. The initial steep decline lasts about 1 min. The amplitude of the drop varies, depending upon the original level, but the relative decrease is about 10 db below the normal amplitude.

The secondary, more gradual decrease lasts longer than the initial drop. The duration is at least 1.5 min. During this time CM declines further and the minimum reached by the end of the secondary decline is from 15 to 20 db below the original normal level.

Guinea pig G-26 which showed no reversal of SP also displayed no rebound of CM, but there was a plateau lasting about 4 min before the responses dropped to lower levels. The CM from the other two animals did rebound after the secondary decline. The interval between the lowest level of CM before the rebound to the peak of the rebound was 2 min and 45 sec in G-47 and 8 min and 45 sec in G-49. The magnitude of this rebound is small. In guinea pig G-49 the peak was 8 μV or 2.3 db above the preceding lowest

level. In G-47 it was only 3 μV or 1.0 db greater than the trough which it follows. These same rebound peaks are 220 μV and 178 μV, or 18.0 db and 17.2 db lower than the original normal amplitude.

Responses persist for a long time after the rebound. In guinea pigs G-47 and G-49 the responses were greater than 15 μV for 25 min after CM began its initial decline.

CM of the pip response parallels exactly the changes of CM of the pure tone responses. Because it is easier to measure the responses to pure tones these responses were chosen to represent the changes in CM shown in Figure IV-8.

2. 2000 cps and 500 cps

The responses to the 2000 cps pips and pure tones show the same qualitative changes with death as were just described for the responses to the 8000 cps pip and pure tone. SP becomes clearly positive in Iv as the AP disappears and CM is declining rapidly. After a period of many minutes SP finally becomes negative. CM exhibits a rebound or temporary increase after a severe initial decrease in amplitude and then shrinks gradually and, in time, completely disappear.

a) tone-pips

The responses in Iv and It to the 2000 cps pip are asymmetrical with respect to the baseline only because of a strong AP (Figure IV-7). The negative phase is strongly

dominant in both scalas. In the three animals used in this set of experiments a positive SP first became clearly evident in Iv after the beginning of the initial decline in CM.

Responses to the 500 cps pip and tone were examined in two animals: in one (G-61) the potentials were observed in Iv and in the other (G-72) the Iv-It arrangement was used. Of course, in the latter arrangement AP was canceled from the responses. In G-61, AP caused the maximum negative voltage, measured from the baseline, to be slightly greater than the maximum positive phase of the largest CM wave. Therefore, the moment when SP became positive could be distinctly observed, about 1 min after the onset of the initial decrease in CM potential. In G-72 the responses were slightly positive to begin with but even so the beginning of the change to greater positivity was distinctly noticeable in 15 sec after the beginning of the fall of CM signaled the death of the animal (Figure IV-8).

The positive SP decreased and then disappeared in 12 min or less after the onset of death in four of the five animals in this group. The positive SP from G-72, however, vanished only after an hour and 15 min.

With stimulation by the 500 cps pip the responses are so small after the positive SP (in Iv) disappears that the final reversal to a negative SP is very difficult to see. However, it has been seen in every animal which was observed for a long enough time. The final reversal of the responses to the 2000 cps pip is less difficult to observe but it is

much less obvious than the final reversal of the responses to the 8000 cps pip.

b) pure tones

The onset of death or the beginning of the rapid decline in the amplitude of CM began in less than 5 min after the injection of the overdose of anesthetic in each of the five animals in these two series. The absolute loss in microvolts in this initial rapid decrease varied greatly, depending on the original normal level, but the relative losses showed a smaller variation. CM dropped by an average of 13.5 db from the original level. The duration of this steep decline varied from 1 min and 10 sec in G-52 to 2 min and 45 sec in G-72.

The slower decline of CM which follows the rapid initial loss lasted about 3 min and the losses beyond that of the initial drop ranged from 3.2 to 8.2 db. This trough in the course of the changes in CM after death varied from 16 to 20 db below the original level.

Temporary increases in the amplitude of CM (rebound) were small but definite in each of the five guinea pigs under discussion. The absolute increases over the lowest levels of responses before the rebound ranged from 3 μV to 11 μV and the relative increases were limited to 1 db or less. The peak of the rebound came between 5 and 10 min after the beginning of the initial decrease in CM.

The duration of the rebound (from the lowest level at the end of the secondary decline in CM to the corresponding

level after the peak of the rebound) was 3 min and 20 sec in G-52 and G-59 and 10 min in G-54. It was only 5.5 sec in G-61 of the 500 cps series but 8 min and 15 sec in G-72 of the same series.

A drop to less than 15 μV was observed only in G-52 of the 2000 cps series. It came 12 min and 30 sec after the onset of death and 5 min and 5 sec after the termination of the rebound (see definition in preceding paragraph). This amplitude was 26 db below the original normal level. The responses from the two animals exposed to the 500 cps pip and tone were not followed long enough to note a level as low as 15 μV. However, a 26 db decrease from the original level was observed at 17 min after the onset of death in G-61 and at 38 min after the same reference time in G-72.

3. General Observations.

The eight animals (three series) discussed do not constitute a sufficiently large sample to give statistical significance to trends in the data derived from them. However, with very few exceptions, all numerical values for a particular measure are commensurate and in many cases they vary very little.

One of the quantitative observations made by Wever, Bray and Lawrence (423) can be confirmed: the peak of the rebound occurs between 5 and 12 min after CM begins to fall.

The observation by Bornschein and Krejci (51) that there is a loss of 10.9 db 5 min after ligature of the aorta was not corroborated by the experiments reported in this section. At 5 min after the beginning of the sharp descent of CM (in experiments of Bornschein and Krejci this began a few seconds after ligature of the aorta) responses were near or beyond the end of the secondary drop in CM in all of the seven animals that showed rebounds. The average loss at that time was about 18 db. However, the animals used by Bornschein and Krejci apparently were hypoxic before they died.

The changes, based on measurements of photographs, which are discussed in this section were seen in at least 20 other guinea pigs. No qualitative differences were seen in any of these animals, although undoubtedly if measurements had been made in all the animals, the ranges of variation would have been considerably extended.

The following observation is without exception: in the response to the 8000 cps pip the AP disappears completely a few seconds after SP vanishes, i.e., just after CM becomes symmetrical with respect to the baseline in Iv and before the responses become predominantly positive. In guinea pigs G-47 and G-49 this moment occurred about 30 sec after the onset of death. The graphs of the amplitude of CM as a function of time show this to be the moment at which CM is falling most rapidly (Figure IV-8). In guinea pigs G-47 and G-49 the SP attained its maximum positive value just

as the steep initial drop began to merge with the slower, secondary decline. The maximum SP relative to the amplitude of CM came as the secondary decline reached its lowest value.

SP in response to the 2000 cps and 500 cps pips also became clearly positive in Iv just as CM began the steepest part of its fall and SP reached a maximum positive value either at the steepest part of the fall or near the end of the initial drop. A maximum relative to CM was reached at various stages of the secondary decline in CM.

The positive SP in response to the 8000 cps pip disappeared shortly after CM began to taper off from the peak of the rebound. For the other pips, the responses also became symmetrical (before the negative state) after the peak of the rebound. This return to symmetry always took longer than the time required by the responses to the 8000 cps pip, but in all cases the return to symmetry occurred after the peak of the rebound.

There were no measurable phase changes of CM for any of the pips during any stage of "death." In addition, the relations between the polarity of the initial CM wave and the acoustic polarity of the initial sound wave at the eardrum remained constant at all times. For scala vestibuli the initial CM wave is negative when the initial acoustic wave is a rarefaction.

No measurements were made of the responses from It during death but without exception the changes in the polarity of SP were exactly opposite to those seen in Iv.

All changes seemed to be otherwise the same in both channels. Because the post-mortem changes viewed from Iv-It were exactly like those from Iv, it is an indication that time relations, at least, were exactly similar in both Iv and It.

AP responses, registered from the Iv + It combination, naturally disappear early: actually in about 30 sec after CM begins to decrease.

4. Responses to Other Pips.

Post-mortem responses to the 3000, 1000, 250 and 100 cps pips have also been observed. Changes in these responses are qualitatively the same as those described for the responses to other pips. SP becomes strongly positive in Iv (negative in It) shortly after CM begins to fail. SP then disappears again and finally reappears with negative sign. This is the typical negative SP which is always detected from Iv in the final stage of the post-mortem responses.

B. Changes during Incomplete Respiratory Failure

In many instances a guinea pig will recover completely after a respiratory failure which has led to the early "post-mortem" changes described above. If SP has been positive (Iv) for more than 1 min, recovery of the animal seldom occurs. However, if the animal recovers before SP has been positive for 1 min the electrical responses usually return to their normal amplitudes and polarities. The course of the regeneration of the responses is the reverse of the pattern of degeneration. Amplitudes increase and the

AP spike (in response to the 8000 cps pip) returns shortly before or just as SP ceases to be positive. For the responses to the 8000 cps pip there is usually a period of supernormality during which the negative SP in Iv or the positive SP in It is more pronounced than normally. The return to normality requires about 3 to 5 min. CM and AP display no obvious supernormality. For the other pips the return to normality, i.e., the recovery after respiratory failure, means a return to symmetry for the responses to the 2000 cps pip and to a smaller positive SP for the responses to the 500 cps pip.

Very often an animal's respiration will fail again after its first recovery and frequently will recover and fail many times before the animal dies. (More than 10 such fluctuations were observed in each of three guinea pigs.) In these cases the electrical responses do not continue to return to their normal amplitudes and polarities. Both CM and AP shrink and SP becomes increasingly negative in Iv, <u>for all pips</u>, both in absolute value and relative to CM. It is of equal interest that after several failures and recoveries (in two instances after only one failure and recovery) successive failures did <u>not</u> bring about reversals of SP for the 8000 cps pip nor induce any positive SP in the responses to the 2000 cps and 500 cps pips. At this stage, failure of respiration leads only to a reduction of CM and AP and to a decrease in the large negative SP (in Iv) but never to a reversal of SP. Recovery increases the responses

and exaggerates the negative SP in Iv and the positive SP in It. After several such partial failures and recoveries, action potentials no longer return when the animal resumes breathing.

This pattern of responses after successive recoveries and failures is also typical of an animal which has been made severely hypoxic but kept alive and finally restored to stable respiration (Figure IV-9). Subsequent post-mortem changes of the responses from an animal in this condition do not include a positive SP in Iv. SP always remains negative.

C. Effect of Lethal Agent

Nitrous oxide or ether were used instead of Dial with urethane to kill some of the animals. Physostigmine, injected intrarterially or in sufficient quantities intraperitoneally, halted the animals' respiration in three other experiments. Some guinea pigs died from operative trauma, even in cases in which bleeding had not been severe. In each of these circumstances the patterns of deterioration of the responses were the same as those described previously when an overdose of Dial with urethane was the lethal agent. When a fluctuating death ensued the same exaggeration of the negative SP in Iv took place and eventually there were no reversals to a positive SP for any of the pips.

Very heavy overdoses of Dial with urethane (G-26) or very large quantities of undiluted nitrous oxide bring about sudden changes, sometimes so rapid that the post-mortem

responses to the 8000 cps pip do not show a reversal to a positive SP in Iv and CM does not rebound but has only a short plateau after the secondary drop. Wever (392) and Bast et al (31) also discuss exceptionally rapid losses of cochlear potentials when death is violent or especially rapid.

D. Other Animals

1. Mammals.

This author has observed post-mortem changes registered from the round window of a cat. Qualitatively all changes were the same as those described for the guinea pig. Fernández and Perlman (personal communication) have also observed these changes in cats.

The writer has also observed the same changes in hamsters (again without measurement) following experiments on these animals by Kahana and Fernández.

2. Pigeons.

Unlike the cochlea of the guinea pig, the pigeon's cochlea is accessible only near its round and oval windows. In experiments on eight pigeons, electrodes were placed either on the RW, in the cochlear recess near the RW, or on the footplate of the columella which fits into the OW. In some experiments two electrodes were used: one on the footplate of the columella and the other either on the RW or in the cochlear recess. The reference electrode was clipped to the muscles of the neck.

The responses to an unfiltered click show the initial CM response to be positive at the RW and cochlear recess and negative at the footplate of the columella when the initial acoustic wave at the eardrum is a rarefaction. These are the same relations that obtain in the guinea pig. Neither CM, AP nor SP could be canceled by adding or subtracting the responses from the electrodes in opposite scalas.

The sensitivity of the pigeon's ear is low. The dynamic range is small and there is no portion of the range above the noise level over which the growth of CM is a linear function of the stimulus strength. CM waves are considerably distorted, even after death (although less so then) when no AP is present.

The pigeon's ear does not respond to the 8000 cps pip. The 3000 cps pip (because of the limitations of the electroacoustic system) was the highest effective pip used in this series of experiments.

The responses to each of the pips (3000, 2000, 1000, 500 and 250 cps) show an asymmetry, the same type of asymmetry designated as SP in the guinea pig's responses. For the 1000, 500, and 250 cps pips SP is positive at the electrode on the RW or in the cochlear recess (both continuous with scala tympani) and at the footplate of the columella (continuous with scala vestibuli).

In response to the 3000 cps and 2000 cps pips SP is always clearly positive at the RW and cochlear recess. At the electrode continuous with scala vestibuli, however, the

initial two or three waves of CM are displaced negatively but the latter part of the baseline is clearly displaced in a positive direction. The positive SP, especially that recorded from scala tympani, is often greater in amplitude than the largest CM wave.

With death, the CM waves of the pip responses become less distorted and the amplitude of the responses declines slowly. SP becomes clearly positive (relative to the neck) at <u>all electrodes</u> for <u>all of the pips used</u>. A second change of SP polarity does not occur. SP always remains positive. Perhaps the responses were not observed over a long enough period for these changes to take place but the potentials seemed to shrink into the baseline noise before any reversals occurred. Further increases in the intensity of the stimulus led only to greater distortion.

PART III. RESPONSES FROM PATHOLOGICAL ANIMALS

The description in the previous section of the pattern of responses from a living guinea pig after prolonged anoxia also applies to the responses from cochleas which have been damaged by: (1) application of KCl to the RW, (2) accoustic trauma, and (3) operative trauma to the cochlea or to the vestibular apparatus (Figure IV-9). In all of the cases CM is greatly reduced and AP is severely damaged or completely absent. On the other hand, SP is negative in Iv and positive in It <u>for all pigs</u> and is more pronounced, at least far more prominent compared to CM and AP than in the normal animal. When a guinea pig in this condition dies all potentials decrease and <u>there are no reversals in the electrical polarity of SP</u>. SP remains negative in Iv and positive in It.

A. <u>Specific Procedures</u>

1. Prolonged Anoxia.

The guinea pigs in this series were deprived of oxygen and were later restored to normal respiration. Respiration was stopped by excessive inhalation of nitrous oxide, ether or chloroform, or by accidental overdoses of Dial with urethane. Intraperitoneal and intrarterial injections of physostigmine suspended respiration in three cases and many times an operative trauma affected the animal's breathing. There was one case of accidental strangulation.

RESPONSES TO 8000 CPS PIP (Iv) AFTER DAMAGE TO COCHLEA

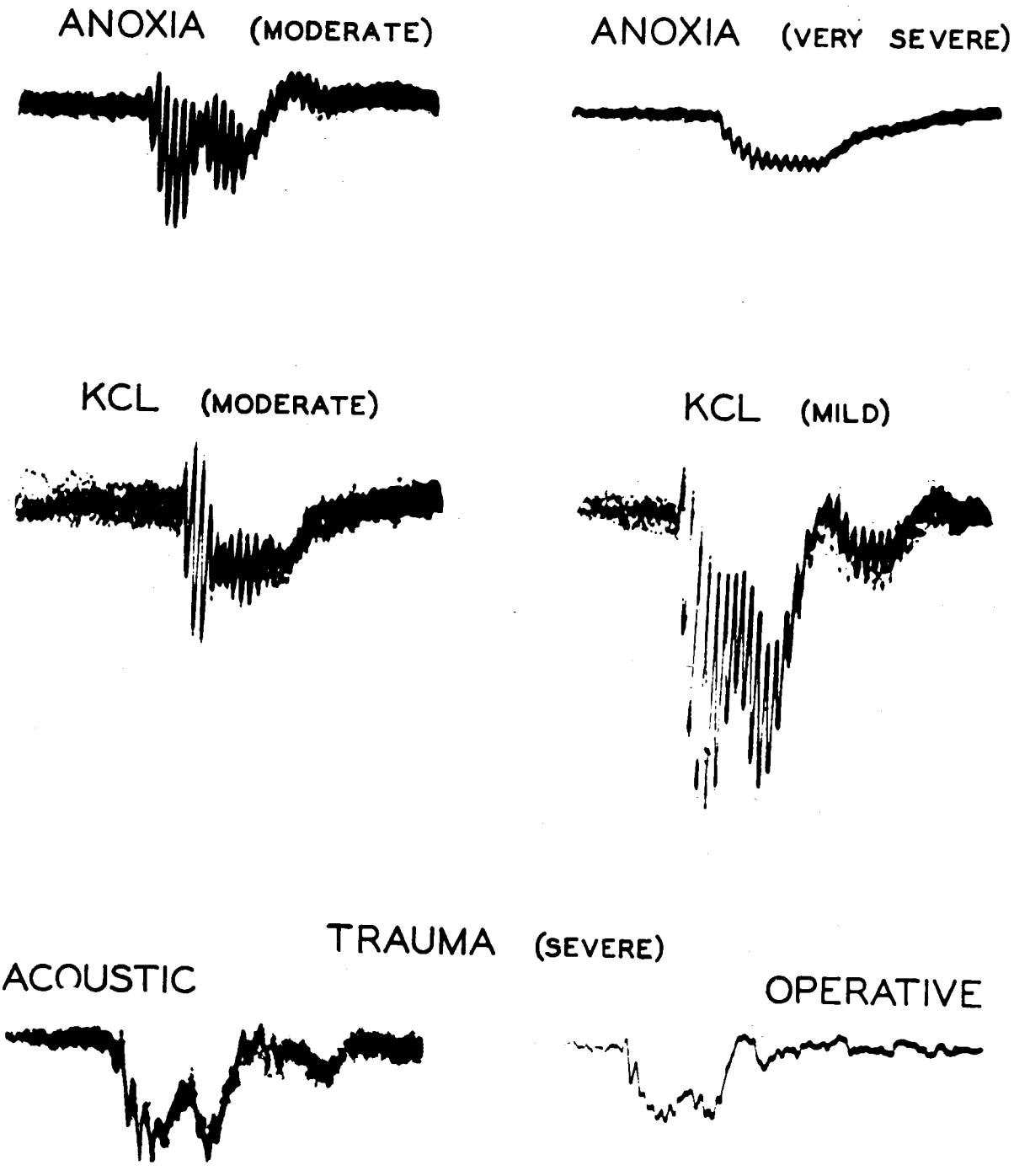


FIGURE IV-9

2. Potassium Chloride.

Several drops of KCl solution were placed on the RW in order to produce changes in the electrical responses. The solutions had to be stronger than 1 N (about 1 gram in 12 cc of distilled water) before the KCl could effect serious damage under the conditions to be described. Naturally, more damage was done with stronger solutions.

A plastic tube (1.5 mm inside diameter) was inserted through a small hole in the bulla and the tube was cemented to the bulla at the edge of the hole. One end of the tube opened directly over the RW; the other extended out through the operative wound. Acoustic conditions apparently were not significantly altered by this tube. The responses remained the same as they had been without the extra hole in the bulla anddid not change when the tube was clamped shut.

A few drops (2 or 3) of the KCl solutions were introduced by the needle of a hypodermic syringe into the plastic tube and consequently onto the RW. Even this small quantity of fluid in the bulla interfered, often seriously, with normal acoustic transmission. Therefore, most of the fluid was withdrawn by suction after a few seconds during which the KCl was allowed to attack the cochlea.

3. Acoustic Trauma.

Observations were made incidental to experiments performed by Davis and his co-workers (149, and unpublished

observations). Trauma was caused by pure tones at sound pressure levels of 150 db or more above 0.0002 microbar. In one experiment the present author produced damage by intense 8000 cps pips presented during several exposures of 2 to 3 minutes.

One animal was tested at least five weeks after it had been exposed for 2 min to a pure tone of 10,000 cps at more than 155 db above 0.0002 microbar. There were no electrical responses from the basal turn for tones of any frequency or intensity. The cochlea of this animal was not saved for microscopic examination. However, two other animals were similarly exposed and kept alive for at least five weeks. Their cochleas were sectioned and microscopic examination showed that the organ of Corti in the entire basal turn was damaged and that the hair cells were the most severely affected structures.

4. Operative Trauma.

The insertion of a needle into scala media often damages the cochlear potentials. Contrary to the other procedures this method never allows even temporary or partial recovery and damage is always severe. Entry into scala media was made either directly through the spiral ligament or indirectly via scala vestibuli or scala tympani. (Entry through the bone into scala vestibuli or scala tympani does not injure the responses. In fact, most of the normal electrode placements were made that way. However, when the holes are so large that fluid pours continuously

from the cochlea there are some changes, but even then the loss of potentials occurs quite slowly.)

B. Nature of Responses after Injury to the Cochlea

1. AP.

For a given intensity of stimulation AP is greatly diminished compared to its amplitude in the normal animal. This is true for tone-pips of all frequencies. AP is often abolished by severe injury. The threshold for AP is regularly raised by more than 30 db after serious damage to the cochlea.

The latency of AP for a given level of the 8000 cps pip is increased. After severe damage AP is detectable only as a small spike superimposed on the falling phase of SP.

2. CM.

After damage to the cochlea CM is also greatly reduced and its threshold is increased. However, the wave form of CM still faithfully reproduces the form of the stimulus. The individual waves still reverse in polarity when the initial acoustic wave at the eardrum is changed from a rarefaction to a condensation or vice versa. When the initial wave at the eardrum is a rarefaction the first CM wave in scala vestibuli is still negative and in scala tympani it is positive. These same relationships are true for the normal animal.

3. SP.

a) 8000 cps pip (Figure IV-9)

If damage to the cochlea has been severe, SP for the 8000 cps pip is also reduced from its normal amplitude at a given intensity. Comparatively, however, the decrease in SP is far less than the losses for AP and CM. In these instances SP is so strong compared to CM that all the CM waves are displaced below the baseline (Iv) except for the positive phase of the first CM wave.

When damage to the cochlea is moderate SP maintains approximately the same amplitude it has in the normal cochlea for the same intensity level. With only mild damage SP is often slightly larger than it is in the normal animal for the same intensity.

Because AP is reduced so much by severe injury it no longer interrupts the course of SP viewed from It or Iv (referred to the neck). SP from Iv now looks like SP from the Iv-It arrangement with just a small AP spike superimposed on it.

b) 3000, 2000, and 1000 cps pips

SP of negative polarity appears in Iv in the responses to the 3000, 2000, and 1000 cps pips when the cochlea has been injured by the procedures previously described. SP is positive in It. SP becomes more pronounced relative to CM and AP as the injury becomes more serious. However, with very severe injury the absolute value of SP also begins to decline. As in the case of the 8000 cps

pip, SP may displace all but the earliest CM wave below the baseline in Iv (above in It) when injury is severe.

c) 500, 250 and 100 cps pips

The responses to the 500, 250 and 100 cps pips in Iv and in Iv-It include a positive SP in the normal animal. This SP disappears after injury to the cochlea and if the damage is severe a strong negative SP appears instead. The changes in SP, CM and AP for the responses to the slower frequency pips are the same as those described for the 8000, 3000 and 2000 cps pips.

C. Changes of Cochlear Potentials during Death after Injury to the Cochlea

1. After Severe Injury.

After the cochlear responses have been altered as severely as described above the polarity of SP does not change when a guinea pig dies. It remains negative in Iv (and positive in It) as long as any responses persist.

Direct observations of the changes of CM with death failed to detect a rebound or temporary recovery of CM after the initial drop in amplitude. However, the potentials were not systematically measured. At this stage before death the CM responses are so diminished from what they are normally that further decreases with death reduce CM to a level at which it is not easily detectable above the baseline noise. To raise the intensity to the point where CM could be more easily measured necessitates getting into the region of considerable distortion both by the equipment and by the animal. However, the writer's observations agree

with those of Wever, Bray and Lawrence (423) and Galambos (162). They also failed to find a rebound after the cochlear responses had been affected by curare injected into the system of the animal. Lawrence and Wever (274) give histological evidence that curare damages the organ of Corti quite severely.

2. After Moderate or Mild Injury.

When the damage is less severe and more AP is still present SP is not quite so pronounced, and CM is not so greatly reduced. Under these circumstances, when the guinea pig dies SP often becomes positive in Iv and finally negative again. However, the positive phase is briefer than when a normal animal dies.

CM does not necessarily rebound but at least a short, stable period exists, a plateau in the course of the decline of CM, while the responses remain at a given level before declining again. Occasionally SP does not reverse but approaches zero and then increases slightly before disappearing completely.

3. General Conclusion.

This much is clear: the greater the apparent damage, i.e., the smaller the AP and CM and the more pronounced the SP, the less likely it is that SP will reverse or even tend to reverse. The relationship is a definite one on this basis. Reversibility or lack of reversibility of SP was predicted correctly for each of about 20 animals before they died.

CHAPTER V

DISCUSSION

The previous chapter served the principal purpose of this dissertation: to describe the behavior of the action potential, the cochlear microphonics, and the summating potential under identical conditions. It was hoped that the data would reveal a functional relationship among these potentials. Because CM always precedes AP the possibility exists that the microphonic is the stimulating agent. However, on the same basis SP can also be regarded as a stimulator. CM and SP exhibit comparable behavior during anoxia. Components of each suffer quickly after respiratory failure and other components of each show greater resistance. The final change in the polarity of SP always occurs after the post-mortem rebound of CM.

However, there are no apparent quantitative relationships among AP, CM or SP, or between any two of them. The pattern of each potential is different and Figures IV-2 through IV-6 show quite plainly that each potential grows at a different rate for the same increases in the sound pressure. When the cochlea is damaged, AP, CM and SP are altered but the changes can be relatively very different for each (Figure IV-9). The changes in amplitude with respiratory failure are also different for each potential.

The second goal of this dissertation is to analyze the summating potential and, if possible, to identify the structures which generate SP.

A. Analysis of Summating Potential

It has been necessary to postulate three separate components for the summating potential in order to explain the normal patterns of responses to tone-pips, the changes in the electrical potentials with death, and the alterations of the response patterns in the damaged cochlea. The components are summarized for scala vestibuli in the following table. The polarities of the components are exactly opposite for scala tympani. In all of the discussion to follow only scala vestibuli will be considered unless there is an indication otherwise.

Table V-1

COMPONENTS OF THE SUMMATING POTENTIAL

pip frequency	A	B	C	SP
8000	- - -	+ + + +	- -	-
2000	- -	+ + + +	- -	0
500	-	+ + + +	- -	+

For each of the pips, two of the three components are the same: B is a large, positive potential and C is a smaller, negative potential. For the 8000 cps pip component A is a large, negative potential. For this frequency A + C is greater than B and therefore the recorded SP is negative. For the 2000 cps pip A + C is equal to B and no SP is apparent in the responses. For the 500 cps pip A + C is less than

B and SP is positive.

When the guinea pig's respiration fails, the negative component A disappears first and for all pips SP becomes definitely positive. Component B suffers next and when it is reduced to the absolute value of the remaining component C the summating potential disappears from the electrical records. When component B shrinks to a level less than that of the negative component C, the summating potential again becomes negative and remains negative.

Apparently components A and B are not only more susceptible to anoxia but also to injury by (a) acoustic overstimulation, (b) by the application of KCl to the round window, and (c) by operative trauma to the cochlea. When A and B are subtracted from the total responses, SP becomes negative for pips of all frequencies. When respiratory failure follows such injury to the cochlea, SP can only decrease. It can no longer reverse.

B. Anatomical Sources of Summating Potential

The behavior of the cochlear potentials which was described in the previous chapter suggests strongly that component A is of neural origin and that the external and internal hair cells of the organ of Corti are responsible for components B and C respectively. However, we have no histopathological evidence to corroborate this hypothesis and most of the supporting evidence is indirect.

1. Component A.

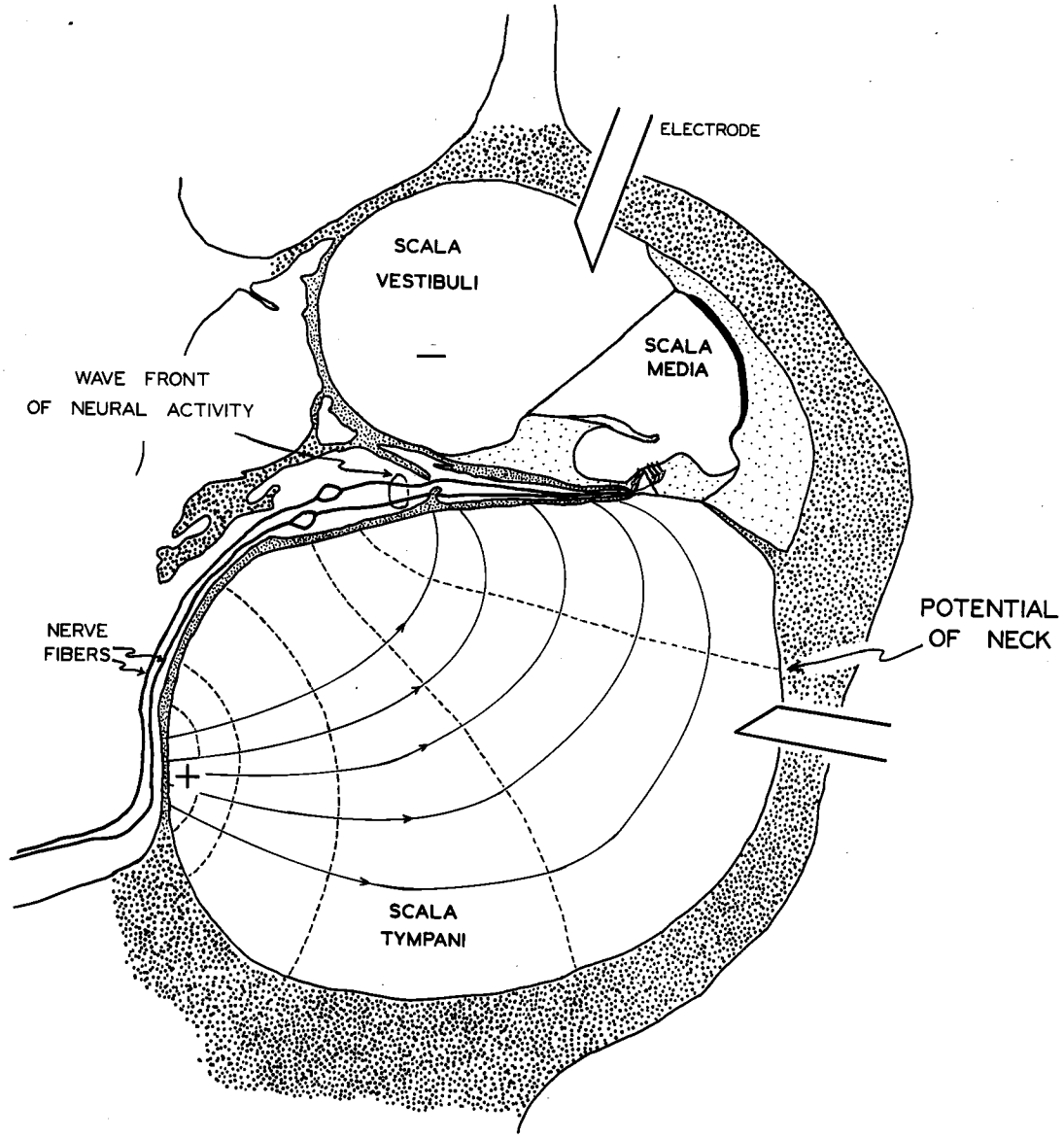
Component A may be attributed to the activity of the nerve fibers in their bony passageways to the modiolus. Very likely this component is an early phase of the action potential which appears before the main spike. There are three bases for this conclusion. (a) Component A is very sensitive to lack of oxygen. (b) There is partial masking of SP for the 8000 cps pip by white noise. (c) There is a large increase in SP for the 8000 cps pip when the electrode is placed closer to the nerve fibers in the modiolus.

Masking of auditory action potentials by noise is a well-established phenomenon. Therefore, it is a natural assumption that the portion of SP masked by the noise is neural in origin. It was not possible to perform successful masking experiments with the 2000 and 500 cps pips because the noise causes considerable unsteadiness in the baseline and the waves of the pip are too greatly separated to permit an estimation of possible changes in the baseline.

When an electrode is placed deep in scala tympani it registers a much larger SP than it records from the superficial position. In the deep position the electrode is closer to the nerve elements in the modiolus. Figure V-1 shows why the deep electrode should register a large, early phase of the action potential and why even the superficial electrodes in scala tympani and scala vestibuli register opposite polarities for this potential.

POTENTIAL FIELD IN BASAL TURN OF COCHLEA

GENERATED BY EARLY PHASE OF ACTION POTENTIAL (8000 CPS PIP)



(CAMERA LUCIDA DRAWING)

→ LINES OF CURRENT FLOW

- - - - - EQUIPOTENTIAL LINES

FIGURE V-1

Table I shows that component A is very strong in the 8000 cps pip response and much less important in the responses to the 2000 and 500 cycle pips. Probably the main cause for this difference is the relative distances from the electrodes of the nerve fibers which discharge in response to these pips. The electrodes in the basal turn are much closer to the region assigned to 8000 cps in most frequency-maps of the cochlea than to the regions of the other frequencies.

2. Components B and C.

As a working hypothesis we assume that the external hair cells are responsible for component B and the internal hair cells for component C. After respiratory failure and the elimination of the more sensitive neural component (A), the summating potential presumably is dominated by the potentials from the EHC. When the EHC finally succumb only the IHC contribute to the summating potential.

With traumatic injury to the cochlea or with the application of KCl to the round window the EHC (source of component B) are assumed to be damaged and only the IHC, (source of component C) and the nerve fibers associated with them (partial source of component A) contribute to SP. The greater susceptibility of EHC to injury of various types is well established (cf. Chapter I, pages 53 and 54). During subsequent respiratory failure there can only be a reduction in components A and C (negative for scala vestibuli).

If the IHC were oriented at an angle of 180° to the EHC it would be easy to suppose that their activity would produce potential fields of opposite electrical polarity at the same recording electrode. However, in the basal coil of the cochlea in the region where the electrodes are inserted the EHC and IHC are inclined at an angle of only about 60° (147). Nevertheless, this orientation is the only obvious reason why two sets of cells which are morphologically very similar could possibly set up opposite potential fields at the same electrodes.

We have no direct information about the potential fields around the hair cells. It has been impossible so far to place an electrode sufficiently deep in scala media to map potential fields in the vicinity of the hair cells without causing severe and permanent losses in the electrical responses. Therefore, at the time of this writing, direct tests of the hair cell hypothesis have not been performed.

The large amplitude of component B from the EHC compared to the smaller component C from the IHC can be explained on three grounds. (a) There are at least three times as many EHC as IHC. (b) The IHC are more protected from the movement, deformation, or other mechanical action which presumably produces the electrical potentials. (c) The EHC are closer to the recording electrodes.

The difference in susceptibility of the EHC and IHC to damage furnishes the strongest argument for the role

of the hair cells in the production of components B and C of the summating potential. Component B, if it is produced by the EHC, can be expected to disappear before component C (from the IHC) after respiratory failure. On this same basis it can be understood why component B should be eliminated by acoustic trauma, etc.

The responses from the pigeon were examined because the pigeon's organ of Corti has only one set of hair cells. There is no tunnel of Corti dividing the sensory cells into two groups and all of the hair cells lie approximately parallel to each other.

Unfortunately, many factors confuse the interpretations of the potentials recorded from the pigeon. Some responses may come from the lagena, that rudimentary organ which lies at the end of the cochlea farthest from the windows. The sensitivity of the cochlea is low and the dynamic range small and there is considerable distortion in the responses. In addition, the electrodes on the footplate of the columella, or on the round window or in the cochlear recess, may not correspond to the positions of the electrodes with respect to the hair cells as they are in the guinea pig's cochlea.

Because of the difficulties outlined above, the comparison of the normal responses of the pigeon to the guinea pig will not be attempted. It was difficult to judge whether or not the neural component A was present in the responses to the pips. However, the changes with death may

be significant. When the pigeon dies there is only one major event: SP which was negative (probably because of the neural component) in scala vestibuli becomes positive and SP in scala tympani which was positive becomes even more pronounced. No further changes in SP were observed. The implication, of course, is that because there is only one set of hair cells there cannot be more than one change at death in the polarity of SP.

C. Analysis of Post-Mortem Rebound of CM

The "rebound" refers to the small, temporary increase in CM following a large decrease in voltage shortly after the cessation of respiration. Galambos's argument for the role of the intraaural muscles in the production of the rebound seems to be sufficiently discounted (cf. Chapter I, pages 28 and 29). There are two other possible explanations for the phenomenon. The first is that there is a brief recovery process in the tissues which produce microphonic voltages during acoustic stimulation. Such a recovery is hardly expected in an animal whose respiration has permanently ceased.

A second explanation for the rebound is based on the premise that the post-mortem CM is being produced by two different elements and that there is a difference in phase between the two components produced by the elements so that the resultant of the two is smaller than either component alone. Thus, it can be assumed that when death subtracts the responses from the more sensitive element, the potential

field at the recording electrode becomes stronger.

The components of the "post-mortem" CM may be compared to components B and C of the summating potential which we have postulated arise in the EHC and IHC respectively. It is possible that the hair cells are the elements which produce CM that is out-of-phase. When the cochlea has been damaged to the extent that SP does not reverse during death there also is no rebound of CM. The damage in those cases presumably affects the EHC more than the IHC (cf. Chapter I and previous discussion).

When the resultant of two vectors is smaller than either vector alone the angle between the vectors is usually close to 180°. (By necessity it is greater than 90°.) Therefore, if the rebound is a result of the subtraction of one component of the post-mortem CM which was reducing the resultant voltage because of its phase difference with the other component, there should be a distinct phase shift in CM during the deterioriation of the potentials (unless phase difference is 180°). No such change was observed (cf. page 101). In addition, the relationship between the polarity of the initial CM wave in response to an acoustic click and the acoustic polarity at the eardrum remains constant during all stages following respiratory failure (cf. page 111). These are the same relationships that hold both for the normal and for the damaged cochlea. If the phase difference were 180° no change of phase would be expected if the weaker of the two vectors disappeared first. However, the weaker effect

is expected from the IHC (see previous section) and the IHC apparently survive the EHC. If the larger vector were to deteriorate first then a null point would be reached when the two vectors achieved the same value.

The relationship between the reversals of SP and the rebound also break down if we consider both to be dependent upon the early deterioration of the external hair cells. We have presumed that the final reversal of SP begins when the output from the EHC falls below that of the IHC. If the rebound of CM results from the removal of the interfering potentials from the EHC, the peak of the rebound should not precede the beginning of the final reversal of SP. However, the peak of the rebound does come first and thus confounds our simple explanation for the rebound. This same observation argues against considering the post-mortem CM as being part of SP, i.e., as being a rapid component whose effects are summated into the slow component, if we adhere to the concept of separate sources for components B and C of the summating potential.

Further speculation on the rebound and on the source of SP should be deferred until a set of chronic experiments can be carried out and supplemented by histo-pathological examinations. Exposure to loud tones is probably the simplest way of damaging the cochlea and with at least one month post-exposure period there would probably be some stable pathology of the organ of Corti. Post-mortem responses should be recorded by a wave-analyzer used as a voltmeter so that

voltages less than 3 μV can be clearly identified. The reversal of SP and the rebound of CM (or lack of both) could then possibly be correlated with the histopathology.

D. Significance of the Cochlear Potentials

1. SP.

Davis, Fernandez and McAuliffe (113) contend that the summating potential "arises in the terminal twigs of the auditory nerve fibers" which are in contact with the base of the hair cells. These authors believe that SP is a non-propagated effect which represents the local excitatory process. The present author is certain that the slow potential that Davis et al observed (see their Figure 3) is the neural component A of SP, described in Section B. If our hypothesis is correct this component of SP cannot be localized to the terminal nerve twigs as a non-propagated reaction. It is a response of the nerves but it is the actual beginning of the propagated disturbance, not its precursor.

One might argue that components B and C actually are non-propagated effects set up in the nerve terminals which cluster at the base of the hair cells. The junctions between the nerves and the hair cells, although not true synapses, are similar to the nerve-to-nerve connections. Conduction across a synapse is severely hampered by anoxia and a definite possibility exists that an excitatory effect from the hair cell to the nerve is equally impeded. Lawrence and Wever (274) recently showed that during anoxia the base

of the hair cells where the nerve filaments cluster is the first part of the hair cell to show signs of degeneration. Even at this stage of anoxia the cochlea was producing CM, although at a reduced level, and we can presume from our own experience that component B or C of the summating potential would have been evident in the responses to tone-pips. It is not probable that an excitatory effect can be set up in the nerve across the region of greatest degeneration after respiratory failure.

2. CM.

The present consensus is that the cochlear microphonics furnish the stimulus for the auditory nerve. The chief proponents of this concept are Wever (392) and de Vries (44, 242, 372, 374). Their evidence is indirect and neither they nor anyone else have presented definite proof that CM is the essential stimulus.

The work of de Vries himself and of van Eyck and others on the microphonics from the vestibular system furnishes a possible argument against the role of these potentials in the stimulation of the nerve. De Vries and his co-workers (242, 372) contend, and rightly, that if the cochlear microphonics provide the stimulus for the auditory nerve, the various extra-cochlear microphonics (ampullar, utricular, saccular, lateral line) should stimulate the nerves of their respective sensory organs. The other organs are closely analagous to the cochlear structures. Each has similar hair cells and a gelatinous mass (tectorial membrane,

cupula, otolithic membrane) which rides over the hairs. However, the extra-cochlear responses to acoustic stimulation, especially the ampullar microphonics, have been elicited only under abnormal conditions. It is necessary to have a fenestra in a semicircular canal in order for the hair cells of the crista to generate microphonics during acoustic stimulation. The problem is of production and not of recording. A penetrating electrode in the semicircular canal does not register microphonics if there is no fenestra in the canal. A similar penetrating electrode in the cochlea is particularly effective.

The vestibular reaction to sound (Tullio effect) after fenestration is not a certain indication that the nerves are stimulated by the concurrent microphonic potentials. The mechanical vibration may very well cause a sufficient deflection of the cupula so that the vestibular reaction to sound is produced by the same mechanism which causes the semicricular canals to react to acceleration.

For the cochlea it has been shown that stimulation is associated with an outward movement of the stapes (cf. Chapter I, page 19). (For high frequencies, 4000 cps and above, the stimulating action is apparently summated over several cycles and no single wave or phase stimulates the nerve (113).) The sensory structures of each semicircular canal also react to movement in one direction only (275, 276, 342). Van Eyck (136) finds, in addition, that during acoustic stimulation of a fenestrated semicircular canal

the action potential spike which is evoked appears earlier when the initial movement of the endolymph by the sound energy is in the direction which stimulates the normal canal during acceleration.

If under normal conditions there is an electrical stimulus for the nerves to the crista of the ampulla it must be virtually a direct current because the customary deflection of the cupula, the adequate stimulus, persists over a long period. There is no repetitive mechanical phenomenon. It is difficult to evaluate the behavior of the cochlea during slow stimulation. Auditory sensitivity decreases at low vibration rates and may not even exist at 1 cycle per second or less. However, there is no direct evidence of movement of the cochlear structures under these conditions so that the effectiveness of a dc microphonic in the cochlea cannot be debated.

Each of the labyrinthine organs apparently is designed to react to a different form of mechanical stimulation but they also appear constructed to translate that energy in the same manner. If the microphonics are the translation of that mechanical energy, then under normal conditions the hair cells of one system are stimulated by a direct current stimulus and the hair cells of a very similar system are stimulated by alternating current. What seems more likely is that in these labyrinthine systems the microphonics and the actual stimulating actions are produced by the same activity. This can account for the parallelism

between CM and auditory function discovered by many investigators and yet makes it possible that the discrepancies between CM and auditory function reported by other authors are real (cf. Chapter I, pages 56 and 57). If the hypothesis of Jielof, Spoor and de Vries (242) for the production of the microphonics is correct (and we have little basis to dispute it), then tension or traction on the hairs of the hair cells of the various organs on which N VIII terminates stimulates the nerve endings in addition to producing the microphonics. This sort of mechanical action is the only one common to the labyrinthine organs and the lateral line organ. The microphonic activity appears (according to the present author) to be an epiphenomenon.

The mode of excitation of the nerves via the hair cells still remains uncertain. At least three actions are possible: (1) mechanical, (2) chemical, and (3) electrical. It is possible that components B and C of the summating potential represent the conversion of the mechanical energy of the acoustic stimulus into a stimulating electrical potential. It is also possible that these components may represent a biological response of greater energy, triggered by the mechanical action. However, there is not sufficient information in the data presented in Chapter IV nor in the reports of previous investigations to provide a satisfactory answer to this question.

CHAPTER VI

SUMMARY

A. Observations

Previous investigations of the cochlear responses to acoustic stimulation have uncovered at least two distinct potentials: the action potential (AP) and the cochlear microphonics (CM). It has been shown that AP results from the activity of the auditory nerve fibers in the cochlea and is greatly dependent on a continuous oxygen supply. CM is the cochlear potential which faithfully reproduces the pattern of the acoustic stimulus. CM, too, demands a continuous oxygen supply but there is another component of CM which persists long after respiration fails. The hair cells of the organ of Corti apparently are the source of both components of CM.

A third potential, the summating potential (SP), has been identified by Davis and his co-workers. SP is obvious only in the responses to tone-pips and appears as a very slow component. The polarity of SP remains constant regardless of changes in the acoustic polarity. Davis and his group found SP less dependent than AP on the oxygen supply and they considered SP at least as hardy as the less sensitive component of CM.

The present investigation compares the behavior of AP, CM, and SP under identical conditions. By canceling out

AP it is possible to view only CM and SP and by canceling CM and SP from the total responses, AP can be measured by itself.

The tone-pip which was the principal acoustic stimulus in these experiments is a series of six or seven waves of the same frequency. The waves build up to a maximum at the third or fourth wave and then taper off at about the same rate. The summating potential is only obvious in the responses to the pips. The action potential is identified far more easily in the responses to tone-pips than in the responses to pure tones.

The experiments confirm the existence of three distinct potentials: AP, CM, and SP. No SP is apparent in the responses to the 2000 cps pip but a slow potential is clearly present in the responses to the 8000 cps and 500 cps pips (Figure IV-1). However, the polarities of SP are opposite for those frequencies. For a pip of given frequency the polarity of SP recorded from scala vestibuli (referred to neck) is opposite to the polarity recorded from scala tympani (referred to neck).

In this study "threshold" is arbitrarily considered to be 3 μV. This is about the smallest potential which can be distinguished from the noise of the baseline. Measurements of absolute thresholds show that the basal turn of the cochlea is far more sensitive to a frequency of 8000 cps than to 2000 cps or 500 cps. There is a general trend towards greater sensitivity in the basal turn to high frequencies. AP thresholds exhibit the same trend. The AP

threshold is significantly lower than the CM threshold for the 8000 cps pip. For the 2000 cps pip, CM and AP have about the same threshold and for the 500 cps pip the CM threshold is appreciably lower than the AP threshold. The threshold for SP is difficult to measure but SP usually is obvious just slightly above the CM threshold.

The increases in AP, CM and SP with increases in sound pressure are all distinctly different, and for pips of different frequencies the growth of each potential is different. CM shows the least variation and for all frequencies it grows at nearly a linear rate with increases of sound pressure. The growth of CM with pure tones is linear. The curves of the voltages of AP and SP as a function of the strength of stimulation approximate power functions but the slopes are distinctly different from unity, usually considerably less (Figure IV-3 to IV-6).

The SP for the 8000 cps pip continues beyond the pip itself. It begins before the start of the AP spike. For the 500 cps pip (and 1000, 250 and 100 cps) the temporal course of SP is that of the envelope of the pip.

An electrode deep in scala tympani of the first turn registers a much larger SP for the 8000 cps pip than the more superficial electrode records. However, there are no differences in the amplitudes of CM or AP. There are no appreciable differences recorded by the deep electrode in AP, CM or SP in the responses to the pips of other frequencies.

White noise presented simultaneously with 8000 cps pip severely masks AP in the response to the pip and reduces SP a little. The amplitude of CM is not affected.

After failure of respiration AP, CM and SP begin to change simultaneously. AP disappears completely within a few seconds. CM decreases rapidly, recovers slightly and then deteriorates further. SP recorded from scala vestibuli of the first turn becomes positive for all pips (including 2000 cps) and then reverses to a final negative state. The polarity of SP in scala tympani is always exactly opposite to that in scala vestibuli.

Insults to the cochlea by anoxia, by acoustic trauma, by KCl on the RW or by operative trauma produce similar alterations of the cochlear potentials (Figure IV-9). CM and AP are reduced and SP becomes negative in scala vestibuli of the first turn (positive in scala tympani) regardless of its original polarity. When respiration fails after the cochlea has been injured all three potentials decrease but SP remains negative. It does not reverse.

B. Interpretations

There are three distinct potentials composing the cochlear potentials: action potential, cochlear microphonics, and summating potential. There are no obvious quantitative relationships among them.

At least two components contribute to CM: one which is very sensitive to lack of oxygen and another which is much less sensitive.

SP is probably the resultant of three components (Chapter V, Table I). Components A and C have the same electrical polarity and component B is opposite. For each of the pips B has the same magnitude. The same is true for C. However, component A is strongest for the high frequency pips and weakest for the lows. Component A is the most sensitive to lack of oxygen and B is next in susceptibility. Component C is the hardiest.

Component A probably arises from the activity of the peripheral nerve fibers in the bony channels which they follow after leaving the organ of Corti and this component is an early phase of the action potential, preceding the large negative spike. Of less certainty is our hypothesis that components B and C arise in the external and internal hair cells respectively.

There are no bases in the observations reported in Chapter IV to question the conclusions of previous investigators that AP arises in the fibers of the auditory nerve in the cochlea and that CM is produced by some action on the hair cells of the organ of Corti.

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